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(71) Applicant *(for all designated States except US)*: TAKEDA CHEMICAL INDUSTRIES, LTD. [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MOMOSE, Yu [JP/JP]; 2-1-213, Sumiregaoka 3-chome, Takarazuka-shi, Hyogo 665 (JP). ODAKA, Hiroyuki [JP/JP]; 12-12, Katsuragi 2-chome, Kita-ku, Kobe-shi, Hyogo 651-12 (JP).

(74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).

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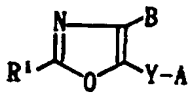
(54) Title: OXAZOLE DERIVATIVES, THEIR PRODUCTION AND USE

(57) Abstract

A novel compound of formula (I), wherein R^1 is a halogen atom, an optionally substituted heterocyclic, hydroxy, thiol or amino group; A is an optionally substituted acyl group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, or an optionally esterified or amidated carboxy group; B is an optionally substituted aromatic group; Y is a divalent aliphatic hydrocarbon group, or a salt thereof, which have an excellent insulin secretion-promoting and blood sugar-depressing effect, and useful in agents for diabetes.



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DESCRIPTION

OXAZOLE DERIVATIVES, THEIR PRODUCTION AND USE

TECHNICAL FIELD

The present invention relates to novel oxazole derivatives which are useful for prophylaxis and therapy of diabetes.

BACKGROUND ART

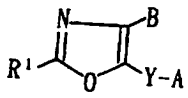
As agents for diabetes, heretofore, various biguanide compounds and sulfonylurea compounds have been used. However, biguanide compounds are not used at present, because these compounds induce undesirable side effects, such as lactic acidosis. Though having an excellent blood sugar-depressing effect, sulfonylurea compounds require care in use since they often induce grave hypoglycemia. Oxazole derivatives having a blood sugar-depressing effect and a sugar tolerance-improving effect are described in, for example, EP-92239, JP59-190979 and EP-382199.

The object of the present invention is to provide novel compounds which have an insulin secretion-promoting effect and a blood sugar-depressing effect, which are useful in agents for diabetes and which have low toxicity.

DISCLOSURE OF INVENTION

The novel oxazole derivatives represented by the following formula (I) have been found to possess an excellent blood sugar-depressing effect and insulin secretion-promoting effect. On the basis of this finding, we have completed the present invention.

Specifically, the present invention provides a compound of the following general formula (I):



(I)

wherein R^1 represents a halogen atom, or an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group;
A represents an optionally substituted acyl group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, or an optionally esterified or amidated carboxy group;
B represents an optionally substituted aromatic group;
Y represents a divalent aliphatic hydrocarbon group, or a salt thereof, and a pharmaceutical composition comprising the compound (I) or a pharmaceutically acceptable salt as an active ingredient.

In the formula (I), the heterocyclic group of the optionally substituted heterocyclic group represented by R^1 or A may be a 5- or 6-membered ring having 1 to 4 atoms selected from N, O and S as the ring-constituting atoms other than carbon atom(s), or a condensed ring thereof. The condensed ring includes, for example, condensed rings comprising the 5- or 6-membered ring as condensed with any of a 6-membered ring having 1 or 2 nitrogen(s), a benzene ring or a 5-membered ring having one sulfur.

Typical examples of the heterocyclic group include aromatic heterocyclic groups such as pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl), pyrimidinyl (e.g. 2-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyridazinyl (e.g. 3-pyridazinyl, 4-pyridazinyl), pyrazinyl (e.g. 2-pyrazinyl), pyrrolyl (e.g. 1-pyrrolyl, 2-pyrrolyl), imidazolyl (e.g. 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), pyrazolyl (e.g. 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl), isoxazolyl, isothiazolyl,

thiazolyl (e.g. 2-thiazolyl, 4-thiazolyl, 5-thiazolyl), oxazolyl (e.g. 2-oxazolyl, 4-oxazolyl, 5-oxazolyl), 1,2,4-oxadiazolyl (e.g. 1,2,4-oxadiazol-5-yl), 1,2,4-triazolyl (e.g. 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl), 1,2,3-triazolyl (e.g. 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl), tetrazolyl (e.g. tetrazol-1-yl, tetrazol-5-yl), benzimidazolyl (e.g. benzimidazol-1-yl, benzimidazol-2-yl), indolyl (e.g. indol-1-yl, indol-3-yl), 1H-indazolyl (e.g. 1H-indazol-1-yl), 1H-pyrrolo[2,3-b]pyrazinyl (e.g. 1H-pyrrolo[2,3-b]pyrazin-1-yl), 1H-pyrrolo[2,3-b]pyridyl (e.g. 1H-pyrrolo[2,3-b]pyridin-1-yl), 1H-imidazo[4,5-b]pyridyl (e.g. 1H-imidazo[4,5-b]pyridin-1-yl), 1H-imidazo[4,5-c]pyridyl (e.g. 1H-imidazo[4,5-c]pyridin-1-yl) and 1H-imidazo[4,5-b]pyrazinyl (e.g. 1H-imidazo[4,5-b]pyrazin-1-yl), and non-aromatic heterocyclic groups such as pyrrolidinyl (e.g. 1-pyrrolidinyl), piperidinyl (e.g. piperidino), morpholinyl (e.g. morpholino), piperazinyl (e.g. 1-piperazinyl), hexamethyleneiminyl (e.g. hexamethyleneimin-1-yl), oxazolidinyl (e.g. oxazolidin-3-yl), thiazolidinyl (e.g. thiazolidin-3-yl, thiazolidin-2-yl), imidazolidinyl (e.g. imidazolidin-3-yl), imidazolinyl (e.g. imidazolin-1-yl, imidazolin-2-yl), oxazolinyl (e.g. oxazolin-2-yl), thiazolinyl (e.g. thiazolin-2-yl), and oxazinyl (e.g. oxazin-2-yl).

Preferred examples of the heterocyclic group are an azolyl group (e.g. pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl), an azolinyl group (e.g. imidazolinyl, oxazolinyl, thiazolinyl), an azolidinyl group (e.g. pyrrolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl).

The heterocyclic group represented by R^1 or A may have 1 to 3 substituents at its substitutable positions. The substituents include, for example, an

aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic group, a halogen atom, a nitro group, an optionally substituted amino group, an optionally substituted acyl group, an optionally substituted hydroxy group, an optionally substituted thiol group, an optionally esterified or amidated carboxy group and oxo group.

Examples of an azolidinyl group substituted by 1 or 2 oxo group(s) are 2-oxoimidazolidinyl (e.g. 2-oxoimidazolidin-1-yl), 2,4-dioxoimidazolidinyl (e.g. 2,4-dioxoimidazolidin-3-yl), 2,4-dioxooxazolidinyl (e.g. 2,4-dioxooxazolidin-3-yl) or 2,4-dioxothiazolidinyl (e.g. 2,4-dioxothiazolidin-3-yl).

The aliphatic hydrocarbon group may be a linear or branched aliphatic hydrocarbon group having 1 to 15 carbon atoms such as, for example, an alkyl group, an alkenyl group and an alkynyl group.

Preferred examples of the alkyl group are alkyl groups having 1 to 10 carbon atoms such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, neopentyl, t-pentyl, 1-ethylpropyl, hexyl, isohexyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl, hexyl, pentyl, octyl, nonyl and decyl.

Preferred examples of the alkenyl group are alkenyl groups having 2 to 10 carbon atoms such as, for example, vinyl, allyl, isopropenyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and 5-hexenyl.

Preferred examples of the alkynyl group are alkynyl groups having 2 to 10 carbon atoms such as, for

example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

The alicyclic hydrocarbon group may be a saturated or unsaturated alicyclic hydrocarbon group having 3 to 12 carbon atoms such as, for example, a cycloalkyl group, a cycloalkenyl group and a cycloalkadienyl group.

Preferred examples of the cycloalkyl group are cycloalkyl groups having 3 to 10 carbon atoms such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl.

Preferred examples of the cycloalkenyl group are cycloalkenyl groups having 3 to 10 carbon atoms such as, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl.

Preferred examples of the cycloalkadienyl group are cycloalkadienyl groups having 4 to 10 carbon atoms such as, for example, 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl.

The aryl group stands for a mono-cyclic or condensed poly-cyclic aromatic hydrocarbon group, and preferred examples of them are aryl groups having 6 to 14 carbon atoms such as, for example, phenyl, naphthyl, anthryl, phenanthryl and acenaphthylenyl. More preferable are phenyl, 1-naphthyl and 2-naphthyl.

Preferred examples of the aromatic heterocyclic group include an aromatic mono-cyclic heterocyclic groups such as furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-

oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl, and an aromatic condensed heterocyclic groups such as benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl.

Preferred examples of the non-aromatic heterocyclic group include oxiranyl, azetidinyl, oxetanyl, thietanyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl and pyrrolidinyl.

Examples of the halogen atom include fluorine, chlorine, bromine and iodine. More preferably are fluorine and bromine.

The optionally substituted amino group may be an amino group ($-NH_2$) which may be mono- or di-substituted with, for example, an alkyl group having 1 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, a cycloalkyl group having 3 to 10 carbon atoms, an acyl group having 1 to 10 carbon atoms (e.g. formyl, C_{1-9} alkyl-carbonyl such as acetyl) or an aromatic group having 6 to 12 carbon atoms (e.g. C_{6-12} aryl such as

phenyl). The substituted amino group includes, for example, methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, acetylamino, propionylamino, benzoylamino, phenylamino and N-methyl-N-phenylamino.

The acyl moiety of the optionally substituted acyl group may be an acyl group having 1 to 13 carbon atoms, including, for example, a formyl group, and a group to be formed by bonding between an alkyl group having 1 to 10 carbon atoms, a cycloalkyl group having 3 to 10 carbon atoms, an alkenyl group having 2 to 10 carbon atoms, a cycloalkenyl group having 3 to 10 carbon atoms or an aromatic group from 6 to 12 carbon atoms and a carbonyl group (e.g., C_{1-10} alkyl-carbonyl such as acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl; C_{3-10} cycloalkyl-carbonyl such as cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl; C_{2-10} alkenyl-carbonyl such as crotonyl; C_{3-10} cycloalkenyl-carbonyl such as 2-cyclohexenecarbonyl; C_{6-10} aryl-carbonyl such as benzoyl, nicotinoyl). The substituent of the substituted acyl group may include, for example, an alkyl group having 1 to 3 carbon atoms, an alkoxy group having 1 to 3 carbon atoms, a halogen atom (e.g., chlorine, fluorine, bromine), a nitro group, a hydroxy group and an amino group.

The substituted hydroxy group of the optionally substituted hydroxy group includes, for example, an alkoxy group, an alkenyloxy group, an aralkyloxy group, an acyloxy group, an aryloxy group, an alkylsulfonyloxy group and an arylsulfonyloxy group.

Preferred examples of the alkoxy group are alkoxy groups having 1 to 10 carbon atoms such as, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, t-butoxy, pentyloxy,

isopentyloxy, neopentyloxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentyloxy and cyclohexyloxy.

Preferred examples of the alkenyloxy group are alkenyloxy groups having 2 to 10 carbon atoms such as, for example, allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy and 2-cyclohexenylmethoxy.

Preferred examples of the aralkyloxy group include aralkyloxy groups having 7 to 10 carbon atoms, for example, phenyl-C_{1-4} alkyloxy group (e.g., benzyloxy, phenethyloxy).

Preferred examples of the acyloxy group include acyloxy groups having 2 to 13 carbon atoms, more preferably alkanoyloxy groups having 2 to 4 carbon atoms (e.g., acetyloxy, propionyloxy, butyryloxy, isobutyryloxy).

Preferred examples of the aryloxy group are aryloxy groups having 6 to 14 carbon atoms such as, for example, phenoxy and naphthyloxy. The aryloxy group may have 1 or 2 substituents such as, for example, a halogen atom (e.g., chlorine, fluorine, bromine), or an alkoxy group having 1 to 4 carbon atoms. The substituted aryloxy group includes, for example, 4-chlorophenoxy and 2-methoxyphenoxy.

Preferred examples of the alkylsulfonyloxy group are alkylsulfonyloxy groups having 1 to 10 carbon atoms such as, for example, methylsulfonyloxy and ethylsulfonyloxy.

Preferred examples of the arylsulfonyloxy are arylsulfonyloxy groups having 6 to 12 carbon atoms (which may be substituted by a C_{1-6} alkyl) such as, for example, phenylsulfonyl, 4-methylsulfonyl.

The substituted thiol group (substituted mercapto group) of the optionally substituted thiol group (optionally substituted mercapto group) includes, for

example, an alkylthio group, an arylthio group, a heteroarylthio group, an aralkylthio group, a heteroarylalkylthio group and an acylthio group.

Preferred examples of the alkylthio group are alkylthio groups having 1 to 10 carbon atoms such as, for example, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, t-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio.

Preferred examples of the arylthio group are arylthio groups having 6 to 14 carbon atoms which may be substituted by a C_{1-6} alkyl group such as, for example, phenylthio, 4-phenylthio and naphthylthio.

The heteroarylthio group includes, for example, thiol groups substituted by any of the above-mentioned aromatic heterocyclic groups. Preferable examples of them are 2-pyridylthio, 3-pyridylthio, 2-imidazolylthio and 1,2,4-triazol-5-ylthio.

Preferred examples of the aralkylthio group are aralkylthio groups having 7 to 10 carbon atoms such as, for example, phenyl-C_{1-4} alkylthio groups (e.g., benzylthio, phenethylthio).

The heteroarylalkylthio group includes, for example, alkylthio groups substituted by any of the above-mentioned aromatic heterocyclic group. The alkylthio moiety of the heteroarylaklylthio group are the same as the above-mentioned alkylthio group. Preferred examples of the heteroarylalkylthio group include pyridyl-C_{1-4} alkylthio groups (e.g., 2-pyridylmethylthio, 3-pyridylmethylthio).

Preferred examples of the acylthio group are acylthio groups having 2 to 13 carbon atoms, more preferably alkanoylthio groups having 2 to 4 carbon atoms (e.g., acetylthio, propionylthio, butyrylthio, isobutytylthio).

The esterified carboxy group of the optionally esterified or amidated carboxy group includes, for example, an alkoxycarbonyl group, an aralkyloxycarbonyl group, an aryloxycarbonyl group and a heteroarylalkyloxycarbonyl.

Preferred examples of the alkoxycarbonyl group are alkoxycarbonyl groups having 2 to 5 carbon atoms such as, for example, C_{1-4} alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and butoxycarbonyl).

Preferred examples of the aralkyloxycarbonyl group are aralkyloxycarbonyl groups having 8 to 10 carbon atoms such as, for example, C_{7-9} aralkyloxy-carbonyl (e.g. benzyloxycarbonyl).

Preferred examples of the aryloxycarbonyl group are aryloxycarbonyl groups having 7 to 15 carbon atoms such as for example, C_{6-14} aryloxy-carbonyl (e.g. phenoxycarbonyl and p-tolyloxycarbonyl).

The heteroarylalkyloxycarbonyl group includes, for example, alkyloxycarbonyl groups substituted with any of the above-mentioned aromatic heterocyclic groups. The alkyloxycarbonyl moiety of the heteroarylalkyloxycarbonyl are the same as the above-mentioned alkoxycarbonyl. Preferred examples of the heteroarylalkyloxycarbonyl group include pyridyl-C_{1-4} alkoxy-carbonyl groups (e.g., 2-pyridylmethoxycarbonyl, 3-pyridylmethoxycarbonyl).

The amidated carboxyl group of the optionally esterified or amidated carboxyl group includes, for example, a group of formula: $-CON(R^5)(R^6)$, wherein R^5 and R^6 may be the same or different and each represents a hydrogen atom, an optionally substituted hydrocarbon group, an optionally substituted hydroxy group or an optionally substituted heterocyclic group. The hydrocarbon groups of the optionally substituted hydrocarbon group represented by R^5 or R^6 includes, for

example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group and an aryl group, which have been referred to hereinabove as the examples of the substituent for the heterocyclic group of R^1 or A. The substituted hydroxy group of the optionally substituted hydroxy group represented by R^5 or R^6 may be the substituted hydroxy group of R^1 or A. The heterocyclic group of the optionally substituted heterocyclic group represented by R^5 or R^6 may be an aromatic heterocyclic group which is referred to hereinabove as the examples of the substituent for the heterocyclic group of R^1 or A. Regarding the substituents of R^5 or R^6, the group may be substituted by 1 to 3 substituents selected from a halogen atom (e.g., chlorine, fluorine, bromine, iodine), an alkyl group having 1 to 4 carbon atoms and an alkoxy group having 1 to 4 carbon atoms.

In the formula (I), an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group or a non-aromatic heterocyclic group for the substituent on the heterocyclic group may be substituted by one or more, preferably 1 to 3 suitable substituents. Such substituents include, for example, an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 2 to 6 carbon atoms, an alkynyl group having 2 to 6 carbon atoms, a cycloalkyl group having 3 to 7 carbon atoms, an aryl group having 6 to 14 carbon atoms (e.g., phenyl, naphthyl), an aromatic heterocyclic group (e.g., thienyl, furyl, pyridyl, oxazolyl, thiazolyl), a non-aromatic heterocyclic group (e.g., tetrahydrofuryl, morpholino, piperidino, pyrrolidino, piperazino), an aralkyl group having 7 to 9 carbon atoms (e.g. benzyl), an amino group, an N-mono(C_{1-4})alkylamino group, an N,N-di(C_{1-4})alkylamino group, an acylamino group having 2 to 8 carbon atoms (e.g., C_{1-7} alkyl-carbonylamino such as acetylamino, propionylamino; benzoylamino), an amidino

group, an acyl group having 2 to 8 carbon atoms (e.g., C_{1-7} alkyl-carbonyl such as acetyl, benzoyl), a carbamoyl group, an N-mono(C_{1-4})alkylcarbamoyl group, an N,N-di(C_{1-4})alkylcarbamoyl group, a sulfamoyl group, an N-mono(C_{1-4})alkylsulfamoyl group, an N,N-di(C_{1-4})alkylsulfamoyl group, a carboxy group, an alkoxycarbonyl group having 2 to 8 carbon atoms, a hydroxy group, an alkoxy group having 1 to 4 carbon atoms, an alkenyloxy group having 2 to 5 carbon atoms, a cycloalkyloxy group having 3 to 7 carbon atoms, an aralkyloxy group having 7 to 9 carbon atoms (e.g. benzyloxy), an aryloxy group having 6 to 14 carbon atoms (e.g., phenyloxy, naphthyloxy), a mercapto group, an alkylthio group having 1 to 4 carbon atoms, an aralkylthio group having 7 to 9 carbon atoms (e.g. benzylthio), an arylthio group having 6 to 14 carbon atoms (e.g., phenylthio, naphthylthio), a sulfo group, a cyano group, an azido group, a nitro group, a nitroso group and a halogen atom (e.g., fluorine, chlorine, bromine, iodine).

In the formula (I), as the halogen atom, the optionally substituted hydroxy group, the optionally substituted thiol group and the optionally substituted amino group represented by R^1, are those that are mentioned hereinabove as the examples of the substituents for the heterocyclic group represented by R^1 or A.

In the formula (I), R^1 is preferably an optionally substituted heterocyclic group.

In the formula (I), as the optionally substituted acyl group, the optionally substituted hydroxy group, and the optionally esterified or amidated carboxy group represented by A are those that are mentioned hereinabove as the examples of the substituents for the heterocyclic group represented by R^1 or A.

In the formula (I), A is preferably an optionally substituted heterocyclic group or an optionally substituted hydroxy group.

In the formula (I), the aromatic group of the optionally substituted aromatic group represented by B includes, for example, an aromatic hydrocarbon group and an aromatic heterocyclic group.

Preferred examples of the aromatic hydrocarbon group are aromatic hydrocarbon groups having 6 to 14 carbon atoms such as for example, C_{6-14} aryl group such as phenyl and naphthyl.

Preferred examples of the aromatic heterocyclic group are those that are mentioned hereinabove as the examples of the substituent for the heterocyclic group represented by R^1 or A. More preferable are furyl, thienyl, pyridyl and quinolyl.

Regarding the optionally substituted aromatic group represented by B, it may be substituted by 1 to 3 substituents selected from, for example, a halogen atom, a nitro group, a cyano group, an optionally substituted alkoxy group, an optionally substituted alkyl group and an optionally substituted cycloalkyl group.

The halogen atom includes, for example, fluorine, chlorine, bromine and iodine.

Examples of the alkoxy group of the optionally substituted alkoxy group are those that are mentioned hereinabove as the examples of the substituent for the heterocyclic group represented by R^1 or A. More preferable are linear or branched alkoxy groups having 1 to 6 carbon atoms.

Examples of the alkyl group of the optionally substituted alkyl group are those that are mentioned hereinabove as the examples of the substituent for the heterocyclic group represented by R^1 or A. More preferable are linear or branched alkyl groups having 1

to 6 carbon atoms.

Examples of the cycloalkyl group of the optionally substituted cycloalkyl group are those that are mentioned hereinabove as the examples of the substituent for the heterocyclic group represented by R^1 or A. More preferable are cycloalkyl groups having 3 to 7 carbon atoms.

Regarding the above-mentioned optionally substituted alkoxy, alkyl and cycloalkyl groups, each of these groups may be substituted by 1 to 3 substituents selected from, for example, a halogen atom (e.g., fluorine, chlorine, bromine, iodine), a hydroxy group and an alkoxy group having 1 to 6 carbon atoms.

The substituted alkoxy group includes, for example, trifluoromethoxy, difluoromethoxy, 2,2,2-trifluoroethoxy and 1,1-difluoroethoxy.

The substituted alkyl group includes, for example, trifluoromethyl, difluoromethyl, 2,2,2-trifluoroethyl, trichloromethyl, 1-hydroxymethyl, methoxymethyl, ethoxymethyl, 2-methoxymethyl and 2,2-dimethoxyethyl.

In the formula (I), B is preferably an optionally substituted aromatic hydrocarbon group, and more preferably an optionally substituted phenyl group.

In the formula (I), the divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms represented by Y may be either linear or branched, and may be either saturated or unsaturated. Typical examples of the aliphatic hydrocarbon group include saturated groups such as $-CH_2-$, $-CH(CH_3)-$, $-(CH_2)_2-$, $-CH(C_2H_5)-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$ and $-(CH_2)_7-$, and unsaturated groups such as $-CH=CH-$, $-C(CH_3)=CH-$, $-CH=CH-CH_2-$, $-C(C_2H_5)=CH-$, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH_2-CH=CH-CH_2-$, $-CH=CH-CH=CH-CH_2-$ and $-CH=CH-CH=CH-CH=CH-CH_2-$. Y is preferably a divalent aliphatic hydrocarbon group having 1 to 4 carbon atoms, and is more preferably the saturated one. Preferred examples

of Y are $-(CH_2)_3-$ and $-(CH_2)_2-$.

Preferred examples of the compound (I) of this invention are as follows.

(1) In the formula (I), R^1 is an optionally substituted heterocyclic group, and a preferred example of the heterocyclic group is a 5- or 6-membered ring having 1 to 4 atoms selected from N, O and S as the ring-constituting atoms other than carbon atom(s), or a condensed ring comprising the 5- or 6-membered ring as condensed with any of a 6-membered ring having 1 or 2 nitrogen, a benzene ring or a 5-membered ring having one sulfur, and a more preferred example of the heterocyclic group is an azolyl group.

(2) In the formula (I), A is an optionally substituted heterocyclic group, preferred example of the heterocyclic group is a 5- or 6-membered ring having 1 to 4 atoms selected from N, O and S as the ring-constituting atoms other than carbon atom(s), or a condensed ring comprising the 5- or 6-membered ring as condensed with a 6-membered ring having 1 or 2 nitrogen, a benzene ring or a 5-membered ring having one sulfur, and more preferred example of the heterocyclic group is an azolyl, azolinyl or azolidinyl group.

(3) In the formula (I), the optionally substituted heterocyclic group represented by R^1 and A is a 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrrolyl, 2-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, isoxazolyl, isothiazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-1-yl, tetrazol-5-yl, benzimidazol-1-yl, benzimidazol-2-yl, indol-1-yl,

indol-3-yl, 1H-indazol-1-yl, 1H-pyrrolo[2,3-b]pyrazin-1-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 1H-imidazo[4,5-b]pyrazin-1-yl, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, hexamethyleneimin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl, imidazolidin-3-yl, imidazolin-1-yl, imidazolin-2-yl, oxazolin-2-yl, thiazolin-2-yl, oxazin-2-yl, 2-oxoimidazolidin-1-yl, 2,4-dioxoimidazolidin-3-yl, 2,4-dioxooxazolidin-3-yl or 2,4-dioxothiazolidin-3-yl group which may be substituted by 1 to 3 substituents selected from the group consisting of an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic group, a halogen atom, a nitro group, an optionally substituted amino group, an optionally substituted acyl group, an optionally substituted hydroxy group, an optionally substituted thiol group and an optionally esterified or amidated carboxy group.

(4) In the formula (I), A is an optionally substituted hydroxy group.

(5) In the formula (I), Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms, and more preferable a divalent aliphatic hydrocarbon group having 2 to 4 carbon atoms.

(6) In the formula (I), R^1 is (i) halogen, (ii) a imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, benzimidazolyl, pyrrolidinyl, piperidinyl, morphorinyl or hexamethyleneiminyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio, (iii) a C_{1-10} alkoxy group, (iv) a C_{6-14} aryloxy group, (v) a C_{1-10} alkylthio group, (vi) a C_{6-14} arylthio which may be substituted by a C_{1-6} alkyl, (vii) a thiol group substituted by an imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl or pyridyl group which may

be substituted by a C_{1-6} alkyl or C_{6-14} aryl, (viii) a pyridyl-C_{1-4} alkylthio group, or (ix) an amino group which may be substituted by 1 or 2 C_{1-10} alkyl or C_{3-10} cycloalkyl;

A is (i) formyl group, (ii) an imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolidinyl, oxazolinyl, thiazolinyl, 2,4-dioxoimidazolidinyl, 2,4-dioxooxazolidinyl or 2,4-dioxothiazolidinyl group which may be substituted by a C_{1-10} alkyl group, (iii) hydroxy group, (iv) a C_{6-14} aryloxy group which may be substituted by a C_{1-4} alkoxy group, (v) a C_{1-10} alkylsulfonyloxy group, (vi) a C_{1-4} alkoxy-carbonyl group, (vii) a C_{7-9} aralkyloxy-carbonyl group, or (viii) a group of the formula: $-CON(R^5)(R^6)$, wherein R^5 and R^6 are independently hydrogen atom, C_{1-10} alkyl which may be substituted by a halogen atom or a C_{1-10} alkoxy group;

B is a phenyl group which may be substituted by a halogen; Y is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

(7) In the formula (I), R^1 is an optionally substituted heterocyclic group; A is an optionally substituted heterocyclic group; and Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms.

(8) In the above-mentioned (7), the heterocyclic group represented by R^1 and A is an azolyl group, an azolinyl group or an azolidinyl group.

(9) In the above-mentioned (7), the heterocyclic group represented by R^1 is an azolyl group, and the heterocyclic group represented by A is an azolyl group, an azolinyl group or an azolidinyl group.

(10) In the above-mentioned (7), R^1 and A are independently a pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl,

tetrazolyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl or thiazolinyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl, C_{1-10} alkylthio and oxo.

(11) In the above-mentioned (7), R^1 is an azolyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio.

(12) In the above-mentioned (11), the azolyl group is an imidazolyl, pyrazolyl, 1,2,4-triazolyl, or 1,2,3-triazolyl group.

(13) In the above-mentioned (7), A is an azolyl, azolinyl or azolidinyl group which may be substituted by 1 or 2 C_{1-10} alkyl or oxo.

(14) In the above-mentioned (7), A is an imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolidinyl, oxazolinyl, thiazolinyl, 2,4-dioxoimidazolidinyl, 2,4-dioxooxazolidinyl or 2,4-dioxothiazolidinyl group which may be substituted by a C_{1-10} alkyl group.

(15) In the above-mentioned (7), B is an optionally substituted phenyl group.

(16) In the above-mentioned (7), B is a phenyl group which may be substiruted by a halogen atom.

(17) In the above-mentioned (7), Y is a divalent aliphatic hydrocarbon group having 3 to 5 carbon atoms.

(18) In the above-mentioned (7), Y is $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$.

(19) In the formula (I), R^1 is an optionally substituted heterocyclic group; A is an optionally substituted hydroxy group; and Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms.

(20) In the above-mentioned (19), the heterocyclic group represented by R^1 is an azolyl

group.

(21) In the above-mentioned (20), the azoyl group is a pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl or tetrazolyl group.

(22) In the above-mentioned (19), R^1 is an azolyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio.

(23) In the above-mentioned (22), the azolyl group is an imidazolyl, pyrazolyl, 1,2,4-triazolyl or 1,2,3-triazolyl group.

(24) In the above-mentioned (19), A is (i) a hydroxy group, (ii) a C_{1-10} alkoxy group, (iii) a C_{2-10} alkenyloxy group, (iv) a C_{7-10} aralkyloxy group, (v) a C_{2-13} acyloxy group, (vi) a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, or (vii) C_{1-10} alkylsulfonyloxy group, and more preferably a hydroxy group.

(25) In the above-mentioned (19), B is an optionally substituted phenyl group, and more preferably a phenyl group which may be substituted by a halogen.

(26) In the above-mentioned (19), Y is a divalent aliphatic hydrocarbon group having 3 to 5 carbon atoms, and more preferably $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$.

(27) In the formula (I), 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol or its salt, 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanol or its salt, 4-(4-chlorophenyl)-5-[3-(1-imidazolyl)propyl]-2-(2-methyl-1-imidazolyl)oxazole or its salt, 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepentanol or its salt, or 4-(4-chlorophenyl)-5-[4-(1-imidazolyl)butyl]-2-(2-methyl-1-imidazolyl)oxazole or its salt.

As the salts of compounds (I) of the present invention, preferred are pharmaceutically acceptable salts thereof, which include, for example, salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids and salts with basic or acidic amino acids. Preferred examples of the salts with inorganic bases include alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts and magnesium salts; and also aluminum salts and ammonium salts. Preferred examples of the salts with organic bases include salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine or N,N'-dibenzylethylenediamine. Preferred examples of the salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid or phosphoric acid. Preferred examples of the salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid or p-toluenesulfonic acid. Preferred examples of the salts with basic amino acids include salts with arginine, lysine or ornithine; and preferred examples of the salts with acidic amino acids include salts with aspartic acid or glutamic acid. Of those salts, the most preferred are sodium salts and potassium salts.

The compounds (I) or their salts of the present invention may also be in the form of hydrates thereof.

The compounds (I) or their pharmaceutically acceptable salts of the present invention (hereinafter referred to as the compounds of the present invention) have a blood sugar lowering effect and an insulin secretion-promoting effect.

The compounds of the present invention can be used, either directly or after having been mixed with any of per-se known, pharmaceutically acceptable carriers, excipients, vehicles and others, as insulin secretion-promoting agents, agents for diabetes, agents for arteriosclerosis, antihyperlipemia, antihypertensive agents, and agents for diabetic complications (e.g., nephropathy, retinopathy, neuropathy), which are applicable to mammals (e.g., humans, mice, rats, rabbits, dogs, cats, bovines, horses, pigs, monkeys).

The compounds of the present invention are of low toxicity. For example, when the compound as obtained in Example 36, as described hereinafter, was orally administered to mice in an amount of 1 g/kg/day, there was no mortality at 5 days.

The compounds of the present invention are orally administered in any form of, for example, tablets, capsules (including soft capsules and microcapsules), powders and granules. As the case may be, however, they may also be parenterally administered for example, as injections, suppositories or pellets. The dose of the compounds of the present invention varies, depending on the objects to which they are administered, the administration routes to be employed, and the conditions to which they are directed to. For example, when they are orally administered to adults, the dose thereof may be desirably from 1 to 500 mg/kg/day, preferably from 10 to 150 mg/kg/day, and it may be administered by dividing into 1 to 3 portions.

The pharmaceutical composition of the present invention can be produced by blending the compound of the invention with pharmaceutically acceptable carriers. The pharmaceutical composition may be produced according to any conventional means that are known in the field of formulations. The pharmaceutical

composition may be in any form of solid preparations such as tablets, capsules, granules or powders, or liquid preparations such as syrups or injections. These can be administered to mammals such as those mentioned hereinabove, either orally or parenterally.

The pharmaceutical composition of the present invention can be used in insulin secretion-promoting agents, agents for diabetes, agents for arteriosclerosis, antihyperlipemia, antihypertensive agents, and agents for diabetic complications (e.g., nephropathy, retinopathy, neuropathy), and is used especially preferably in insulin secretion-promoting agents and agents for diabetes.

And the compound (I) of the present invention can be given, to the same object, agents for diabetes, agents for diabetic complications, antihyperlipemia or antihypertensive agents at the same time or time lag.

Examples of the agents for diabetes are insulin sensitivity-increasing agents (e.g. pioglitazone, troglitazone, BRL-49653, etc.), α-glucosidase inhibitor (e.g. voglibose, acarbose, miglitol, etc.) and so on. Examples of the agents for diabetic complications are aldose reductase inhibitor (e.g. tolrestat, epalrestat, zenarestat, etc.) and so on. Examples of the antihyperlipemia are statins such as cholesterol-biosynthesis inhibitor (e.g. pravastatin, simvastatin, lovastatin, cerivastatin, etc.), squalene synthetase inhibitor or fibrates having triglyceride lowering effect (e.g. bezafibrate, etc.). Examples of the antihypertensive agents are angiotensin converting enzyme inhibitor (e.g. captopril, enalapril, delapril, etc.), angiotensin II antagonist (e.g. losartan, candesartan, cilexetil, etc.) and so on.

The pharmaceutically acceptable carriers include various conventional, organic or inorganic carrier substances that are commonly used for formulation

matter. For example, for solid preparations, employable carriers are excipients, lubricants, binders and disintegrators; and for liquid preparations, employable carriers are solvents, dissolution aids, suspending agents, isotonizing agents, buffers and analgesics. If desired, further employable carriers are any other pharmaceutical additives such as preservatives, antioxidants, colorants and sweeteners.

Preferred examples of excipients include lactose, white sugar, D-mannitol, starch, crystalline cellulose and light silicic acid anhydride.

Preferred examples of lubricants include magnesium stearate, calcium stearate, talc and colloidal silica.

Preferred examples of binders include crystalline cellulose, white sugar, D-mannitol, trehalose, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and polyvinyl pyrrolidone.

Preferred examples of disintegrators include starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium cross-carmellose and sodium carboxymethyl starch.

Preferred examples of solvents are water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and tricaprylin.

Preferred examples of dissolution aids include polyethylene glycol, propylene glycol, D-mannitol, trehalose, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Preferred examples of suspending agents include surfactants such as stearyltriethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glycerol monostearate; and also hydrophilic polymers such as polyvinyl alcohol, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, methyl cellulose,

hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Preferred examples of isotonizing agents include sodium chloride, glycerin and D-mannitol.

Preferred examples of buffers include those of phosphates, acetates, carbonates or citrates.

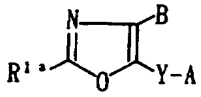
A preferred example of analgesics is benzyl alcohol.

Preferred examples of preservatives include parahydroxybenzoates, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

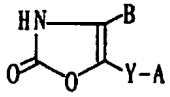
Preferred examples of antioxidants include sulfites, and ascorbic acid.

The compounds (I) of the present invention can be produced by per-se known methods. For example, the compounds (I) of the invention can be produced by the methods mentioned hereinafter or according to these, or by the methods described in EP-92239 and JP59-190979 or according to those methods.

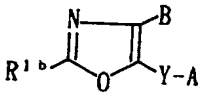
In the formula (I), a compound represented by the formula (I-a):



wherein R^{1a} is a halogen atom, and the other symbols are of the same meanings as defined above, or a salt thereof can be produced by reacting a compound represented by the formula:



wherein all symbols are of the same meanings as defined above, or a salt thereof with a halogenating agent, and a compound represented by the formula (I-b):

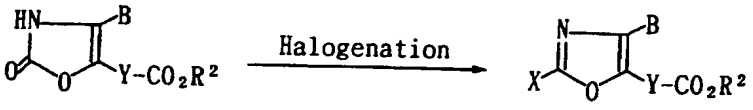


wherein R^{1b} is an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group, corresponding to R^1, and the other symbols are of the same meanings as defined above, or a salt thereof can be produced by reacting a compound (I-a) or a salt thereof with a compound represented by the formula:

$$R^{1b}\text{-}H$$

wherein all symbols are of the same meanings as defined above, or a salt thereof.

Method A:



(II) (I-1)

wherein R^2 represents an alkyl group having 1 to 5 carbon atoms; X represents a halogen atom; and the others are of the same meanings as mentioned above.

The alkyl group having 1 to 5 carbon atoms, represented by R^2 may include those having 1 to 5 carbon atoms of the examples of the alkyl group as referred to herein above for the substituent for the heterocyclic group of R^1 or A.

The halogen atom represented by X includes, for example, chlorine, fluorine and bromine.

Compounds (I-1) which correspond to compounds (I) where R^1 is a halogen atom and A is an esterified carboxyl group, can be produced, for example, by halogenation of compounds (II). This reaction may be

conducted generally in the presence of a halogenating agent in a solvent that does not have any influence on the reaction. If desired, an excess amount of such a halogenating agent can be used for the solvent to effect the reaction.

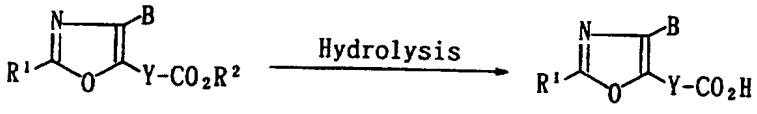
The halogenating agent includes, for example, phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, thionyl chloride and phosphorus tribromide. The amount of the halogenating agent to be used may be from 1 to 10 molar equivalents, preferably from 3 to 6 molar equivalents, relative to the compound (II).

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; pyridine; and mixed solvents of these.

The reaction temperature ranges generally from 20 to 180°C, preferably from 50 to 130°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-1) thus produced may be isolated and purified through any ordinary separating and isolating means, for example, through concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method B:



(I-2) (I-3)

wherein all symbols are of the same meanings as mentioned above.

Compounds (I-3) which correspond to compounds (I) where A is a carboxyl group, can be produced, for

example, by hydrolysis of compounds (I-2). This reaction may be conducted in any ordinary manner, for example, in the presence of a base or an acid in an aqueous solvent.

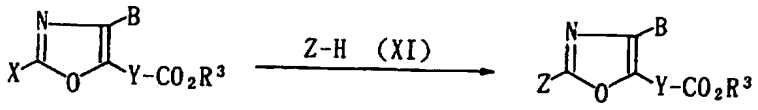
The aqueous solvent may be a mixed solvent comprising water and any of alcohols (methanol and ethanol), ethers (e.g. tetrahydrofuran and dioxane), dimethylsulfoxide and acetone.

The acid includes, for example, hydrochloric acid, sulfuric acid, acetic acid and hydrobromic acid. The base includes, for example, potassium carbonate, sodium carbonate, sodium methoxide, potassium hydroxide, sodium hydroxide and lithium hydroxide. It is desirable that the acid or base to be used is excess over the compound (I-2) (for example, from about 1.2 to about 5 equivalents of the base, or from about 2 to about 50 equivalents of the acid).

The reaction temperature ranges generally from -20°C to 150°C, preferably from -10°C to 100°C. The reaction time ranges from 0.1 to 20 hours.

The compounds (I-3) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method C:



(I-4) (I-5)

wherein R^3 represents a hydrogen atom or an alkyl group having 1 to 5 carbon atoms; Z represents an optionally substituted heterocyclic, hydroxy, thiol or amino

group; and the other symbols are of the same meanings as mentioned above.

The alkyl group having 1 to 5 carbon atoms, represented by R^3 may include those having 1 to 5 carbon atoms as referred to hereinabove for the examples of the alkyl group to be the substituent for the heterocyclic group of R^1 or A.

The optionally substituted heterocyclic, hydroxy, thiol or amino group which are represented by Z may include those as referred to hereinabove for the optionally substituted heterocyclic, hydroxy, thiol or amino group of R^1.

Compounds (I-5) which correspond to compounds (I) where R^1 is an optionally substituted heterocyclic, hydroxy, thiol or amino group, and A is an optionally esterified carboxy group, can be produced, for example, by reacting a compound (I-4) with a compound (XI). This reaction may be effected generally in the presence of a base in a solvent that does not have any influence on the reaction. Where Z is an optionally substituted amino group in the compound (XI), an excess amount of said compound (XI) can be used as the solvent.

The solvent that does not have any influence on the reaction includes, for example, alcohols such as methanol and ethanol; ethers such as tetrahydrofuran and dioxane; N,N-dimethylformamide, dimethylsulfoxide, acetone, water; and mixed solvents of these.

The base includes, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; metal hydrides such as sodium hydride; sodium ethoxide, and sodium methoxide.

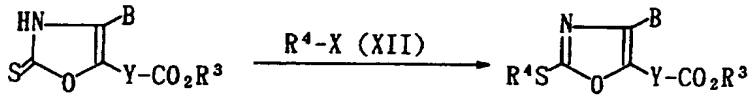
The amount of the compound (XI) to be used may be generally from about 1 to about 10 molar equivalents relative to the compound (I-4). Where Z is an optionally substituted amino group in the compound

(XI), the amount of the compound (XI) to be used may be generally from about 1 to about 50 molar equivalents relative to the compound (I-4).

The reaction temperature ranges generally from 20 to 180°C, preferably from 80 to 140°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-5) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method D:



(III) (I-6)

wherein R^4 represents an alkyl, aralkyl, heteroarylalkyl or acyl group; and the other symbols are of the same meanings as those mentioned above.

The alkyl, aralkyl, heteroarylalkyl or acyl group represented by R^4, include the alkyl, aralkyl, heteroarylalkyl or acyl group of the alkylthio, aralkylthio, heteroarylalkylthio or acyl group that has been mentioned hereinabove for the optionally substituted thiol group of R^1.

Compounds (I-6) which correspond to compounds (I) where R^1 is a substituted thiol group, and A is an optionally esterified carboxy group, can be produced, for example, by reacting a compound (III) with a compound (XII). This reaction may be conducted in the presence of a base in a solvent that does not have any influence on the reaction.

The base includes, for example, alkali metal salts

such as potassium hydroxide, sodium hydroxide, lithium hydroxide, potassium carbonate, sodium carbonate and sodium hydrogencarbonate; metal hydrides such as sodium hydride; sodium methoxide, and sodium ethoxide.

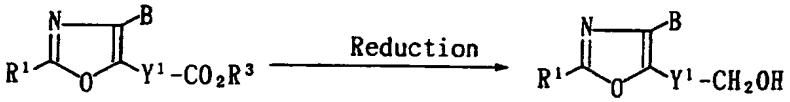
The solvent that does not have any influence on the reaction includes, for example, ethers such as tetrahydrofuran and dioxane; aromatic hydrocarbons such as toluene and xylene; N,N-dimethylformamide, dimethylsulfoxide, acetone, water; and mixed solvents of these.

The amount of the compound (XII) to be used may be from about 1 to about 10 molar equivalents relative to the compound (III).

The reaction temperature ranges generally from -20°C to 150°C, preferably from about 0 to about 100°C. The reaction time ranges from 0.1 to 20 hours.

The compounds (I-6) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method E:



(I-7) (I-8)

wherein Y^1 represents a divalent aliphatic hydrocarbon group; and the other symbols are of the same meanings as those mentioned above.

Y^1-CH_2 represents a divalent aliphatic hydrocarbon group represented by the above-mentioned Y.

Compounds (I-8) which correspond to compounds (I) where A is a hydroxyl group, can be produced, for

example, by reduction of compounds (I-7). This reaction may be conducted in any per-se known manner. Generally using a reducing agent, the reduction may be conducted in a solvent that does not have any influence on the reaction.

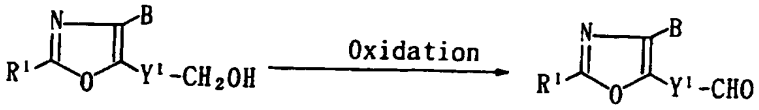
The reducing agent to be used includes, for example, metal hydrides such as alkali metal borohydrides (e.g., sodium borohydride, lithium borohydride), metal-hydrogen complexes (e.g. lithium aluminium hydride), organic tin compounds (e.g. triphenyl tin hydride), diborane, and substituted boranes.

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; halogenated hydrocarbons such as chloroform, dichloromethane and carbon tetrachloride; ethers such as tetrahydrofuran and dioxane; alcohols such as methanol and ethanol; N,N-dimethylformamide; and mixed solvents of these. These solvents may be suitably selected, depending on the type of the reducing agent used.

The reaction temperature ranges generally from -20°C to 150°C, preferably from about 0 to about 100°C. The reaction time ranges from 0.1 to 10 hours.

The compounds (I-8) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method F:



(I-8) (I-9)

wherein all symbols are of the same meanings as those mentioned above.

Compounds (I-9) which correspond to compounds (I) where A is a formyl group, can be produced, for example, by oxidation of compounds (I-8). This reaction may be conducted in any per-se known manner. The oxidation may be effected, for example, with manganese dioxide, chromic acid, dimethylsulfoxide or the like.

Where the oxidation is conducted with dimethylsulfoxide, the reaction may be conducted in the presence of an electrophilic reagent in a solvent that does not have any influence on the reaction.

The electrophilic reagent includes, for example, acetic anhydride, phosphoric anhydride, oxalyl chloride, dicyclohexylcarbodiimide and chlorine. The amount of the electrophilic reagent to be used may be generally an equimolar amount relative to dimethylsulfoxide.

The solvent that does not have any influence on the reaction includes, for example, halogenated hydrocarbons such as chloroform and dichloromethane; and aromatic hydrocarbons such as benzene, and toluene.

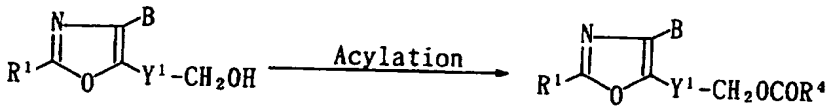
The amount of dimethylsulfoxide to be used may be from 1 to 5 molar equivalents, preferably from 1 to 2 molar equivalents, relative to the compound (I-8).

The reaction temperature ranges generally from -20°C to 100°C, preferably from about 0 to about 60°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-9) thus produced may be isolated

and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer chromatography or the like.

Method G:



(I-8) (I-10)

wherein all symbols are of the same meanings as those mentioned above.

Compounds (I-10) which correspond to compounds (I) where A is a substituted hydroxy group, can be produced, for example, by acylation of compounds (I-8). This reaction may be conducted in any per-se known manner. The acylation may be effected, for example, according to a method of directly condensing the compound (I-8) with a carboxylic acid derivative (R^4CO_2H), using a dehydrating agent (e.g., dicyclohexylcarbodiimide), or according to a method of suitably reacting the compound (I-8) with a reactive derivative of such a carboxylic acid derivative (R^4CO_2H). The reactive derivative of a carboxylic acid derivative (R^4CO_2H) includes, for example, acid anhydrides, acid halides (e.g., acid chlorides, acid bromides), imidazolides, and mixed acid anhydrides (e.g., anhydrides with methyl carbonate, ethyl carbonate or isobutyl carbonate).

Of these, the most simple method is to use such an acid chloride or acid anhydride, in which the intended reaction is conducted in the presence of a base in a solvent that does not have any influence on the reaction.

The base includes, for example, triethylamine, N-methylmorpholine, N,N-dimethylaniline, sodium hydrogencarbonate, potassium carbonate and sodium carbonate.

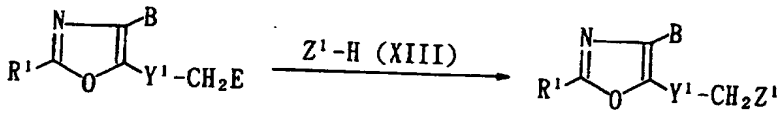
The solvent that does not have any influence on the reaction includes, for example, halogenated hydrocarbons such as chloroform and dichloromethane; aromatic hydrocarbons such as benzene and toluene; ethyl acetate; and tetrahydrofuran.

The amount of the acid chloride or acid anhydride to be used may be from about 1 to about 5 molar equivalents relative to the compound (I-8).

The reaction temperature ranges from about -30°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-10) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method H:



(IV: E is halogen)
(I-20: E is OSO_2R^4)

(I-11)

wherein E represents a halogen atom or OSO_2R^4; Z^1 represents an optionally substituted heterocyclic or hydroxy group; and the other symbols are of the same meanings as those mentioned above.

The halogen atom represented by E includes, for example, chlorine, fluorine and bromine atoms.

The optionally substituted heterocyclic or hydroxy

group represented by Z^1 may include the examples of the optionally substituted heterocyclic or hydroxy group as referred to hereinabove for R^1.

Compounds (I-11) which correspond to the compounds (I) where A is an optionally substituted heterocyclic or hydroxy group, can be produced, for example, by condensation of a compound (IV or I-20) with a compound (XIII). This reaction may be conducted in any ordinary manner, in the presence of a base in a solvent that does not have any influence on the reaction.

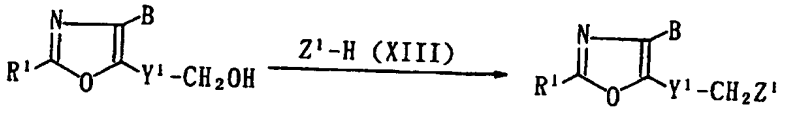
The base includes, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate and potassium carbonate; amines such as pyridine, triethylamine and N,N-dimethylaniline; metal hydrides such as potassium hydride and sodium hydride; sodium methoxide, sodium ethoxide, and potassium t-butoxide. The amount of the base to be used may be preferably from 1 to 5 molar equivalents relative to the compound (IV or I-20).

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran and dioxane; ketones such as acetone and 2-butanone; halogenated hydrocarbons such as chloroform and dichloromethane; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The reaction temperature ranges generally from -50°C to 150°C, preferably from about -10°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-11) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method I:



(I-8) (I-11)

wherein all symbols are of the same meanings as those mentioned above.

Compounds (I-11) which correspond to the compounds (I) where A is an optionally substituted heterocyclic or hydroxy group, can be produced, for example, by condensation of a compound (I-8) with a compound (XIII). This reaction may be conducted in any ordinary manner, in the presence of an organic phosphorus compound and an electrophilic reagent in a solvent that does not have any influence on the reaction.

The organic phosphorus compound includes, for example, triphenylphosphine and tributylphosphine. The electrophilic reagent includes, for example, diethyl azodicarboxylate, diisopropyl azodicarboxylate and azodicarbonylpiperazine. The amount of the organic phosphorus compound and that of the electrophilic reagent may be preferably from 1 to 5 molar equivalents each, relative to the compound (I-8).

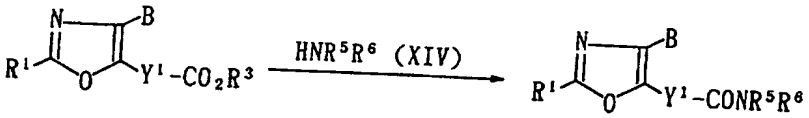
The solvent that does not have any influence on the reaction includes, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as chloroform and dichloromethane; aromatic hydrocarbons such as benzene, toluene and xylene; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The reaction temperature ranges generally from -50°C to 150°C, preferably from about -10°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-11) thus produced may be isolated

and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method J:



(I-7) (I-12)

wherein all symbols are of the same meanings as those mentioned above.

Compounds (I-12) which correspond to the compounds (I) where A is an amidated carboxy group, can be produced, for example, by reacting a compound (I-7) with a compound (XIV).

Where R^3 is an alkyl group having 1 to 5 carbon atoms in the compound (I-7), the reaction may be conducted in the presence of a solvent that does not have any influence on the reaction or in the presence of no solvent.

The solvent that does not have any influence on the reaction includes, for example, alcohols such as methanol and ethanol; aromatic hydrocarbons such as toluene and xylene; pyridine, N,N-dimethylformamide, and dimethylsulfoxide.

The amount of the compound (XIV) to be used is preferably an excess one over the compound (I-7).

The reaction temperature ranges from 20 to 200°C, and the reaction time ranges from 0.1 to 20 hours.

Where R^3 is a hydrogen atom in the compound (I-7), the reaction may be conducted according to a method of directly condensing the compound (I-7) with the compound (XIV) in the presence of a dehydrating agent

(e.g., dicyclohexylcarbodiimide), or a method of suitably reacting a reactive derivative of the compound (I-7) with the compound (XIV). In this reaction, the reactive derivative of the compound (I-7) includes, for example, acid anhydrides, acid halides (e.g., acid chlorides, acid bromides), imidazolides, and mixed acid anhydrides (e.g., anhydrides with methyl carbonate, ethyl carbonate or isobutyl carbonate).

Of these, the most simple method is to use such an acid halide or mixed acid anhydride.

For example, when an acid halide is used, the reaction may be conducted in the presence of a base in a solvent that does not have any influence on the reaction.

The base includes, for example, triethylamine, N-methylmorpholine, N,N-dimethylaniline, sodium hydrogencarbonate, potassium carbonate, and sodium carbonate.

The solvent that does not have any influence on the reaction includes, for example, halogenated hydrocarbons such as chloroform and dichloromethane; aromatic hydrocarbons such as benzene and toluene; ethyl acetate, tetrahydrofuran, water; and mixed solvents of these.

The amount of the compound (XIV) to be used may be from about 1 to about 1.5 molar equivalents relative to the compound (I-7).

The reaction temperature ranges from about -30°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

On the other hand, where a mixed acid anhydride is used, the compound (I-7) is first reacted with a chlorocarbonate (e.g., methyl chlorocarbonate, ethyl chlorocarbonate, or isobutyl chlorocarbonate) in the presence of a base (e.g., triethylamine, N-methylmorpholine, N,N-dimethylaniline, sodium

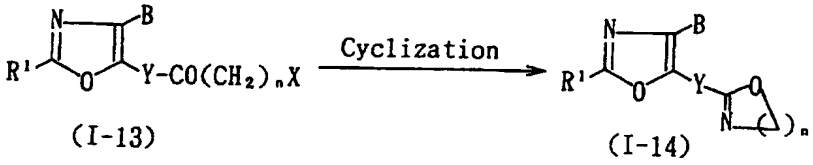
hydrogencarbonate, potassium carbonate, sodium carbonate), and then reacted with the compound (XIV). The amount of the compound (XIV) to be used may be from about 1 to about 1.5 molar equivalents relative to the compound (I-7).

This reaction may be conducted in a solvent that does not have any influence on the reaction. Such an inert solvent includes, for example, halogenated hydrocarbons such as chloroform and dichloromethane; aromatic hydrocarbons such as benzene and toluene; ethyl acetate, tetrahydrofuran, water; and mixed solvents of these.

The reaction temperature ranges from about -30°C to about 50°C, and the reaction time ranges from 0.5 to 20 hours.

The compounds (I-12) thus produced may be isolated and purified through any ordinary separating and isolating means, for example, through concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, trans-solvation, chromatography or the like.

Method K:



(I-13) (I-14)

wherein n represents 2 or 3; and the other symbols are of the same meanings as those mentioned above.

Compounds (I-14) which correspond to the compounds (I) where A is a heterocyclic group, can be produced, for example, through cyclization of a compound (I-13).

This reaction may be conducted in the presence of a base in a solvent that does not have any influence on the reaction.

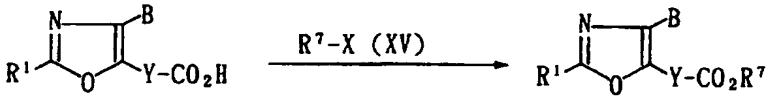
The base includes, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate and potassium carbonate; amines such as pyridine, triethylamine and N,N-dimethylaniline; metal hydrides such as potassium hydride and sodium hydride; sodium methoxide, sodium ethoxide, and potassium t-butoxide. The amount of the base to be used may be preferably from 1 to 5 molar equivalents relative to the compound (I-13).

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran and dioxane; ketones such as acetone and 2-butanone; halogenated hydrocarbons such as chloroform and dichloromethane; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The reaction temperature ranges generally from -50°C to 150°C, preferably from about -10°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-14) thus produced may be isolated and purified through any ordinary separating and isolating means, for example, through concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, trans-solvation, chromatography or the like.

Method L:



(I-3) (I-15)

wherein R^7 represents an alkyl, aralkyl, aryl or heteroarylalkyl group; and the other symbols are of the same meanings as those mentioned above.

The alkyl, aralkyl, aryl or heteroarylalkyl group to represented by R^7, include the examples of the alkyl, aralkyl, aryl or heteroarylalkyl moiety of the esterified carboxy group, or that is, the alkoxycarbonyl, aralkyloxycarbonyl, aryloxycarbonyl or heteroarylalkyloxycarbonyl group, that have been mentioned hereinabove for the substituent for R^1 or A.

Compounds (I-15) which correspond to the compounds (I) where A is an esterified carboxy group, can be produced, for example, by reacting a compound (I-3) with a compound (XV). This reaction may be conducted in any ordinary manner, in the presence of a base in a solvent that does not have any influence on the reaction.

The base includes, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium hydrogencarbonate, potassium carbonate and sodium carbonate; metal hydrides such as sodium hydride; sodium methoxide, and sodium ethoxide.

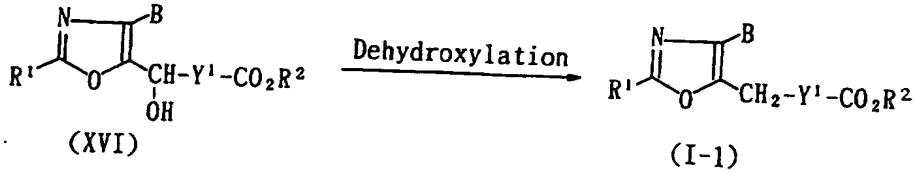
The solvent that does not have any influence on the reaction includes, for example, ethers such as tetrahydrofuran and dioxane; ketones such as acetone and 2-butanone; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The amount of the compound (XV) to be used may be preferably from about 1 to about 10 molar equivalents relative to the compound (I-3).

The reaction temperature ranges generally from -20°C to 150°C, preferably from about 0°C to about 100°C. The reaction time ranges from 0.5 to 20 hours.

The compounds (I-15) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method M:



(XVI) (I-1)

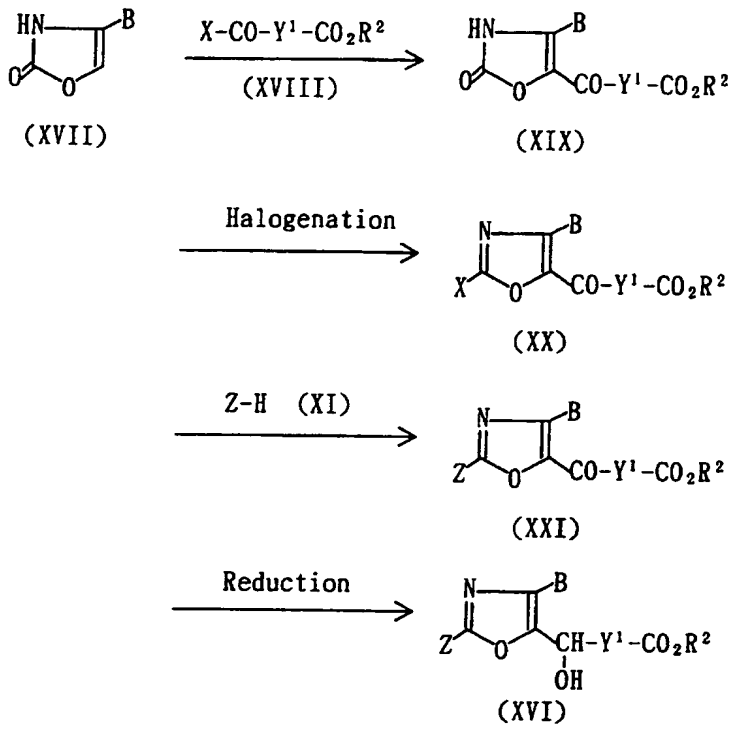
wherein all symbols are of the same meanings as those mentioned above.

The compound (I-16) can be produced by dehydroxylation of the compound (XVI). In this method, the compound (XVI) is directly reduced by silane, or the hydroxy group on the compound (XVI) is halogenated and further reduced. The reduction with silane is promoted by reaction with the compound (XVI) and triethylsilane or diethylsilane in trifluoro acetic acid. The halogenating agent includes, for example, thionyl chloride and phosphorus tribromide. For the reducing agent, metals such as iron, zinc are preferably used in hydrochloric acid or acetic acid.

The compounds (I-16) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extration, precipitation, recrystallization, phasic transfer, chromatography or the like.

The starting compounds(XVI) can be produced by the folowing Method N.

Method N:

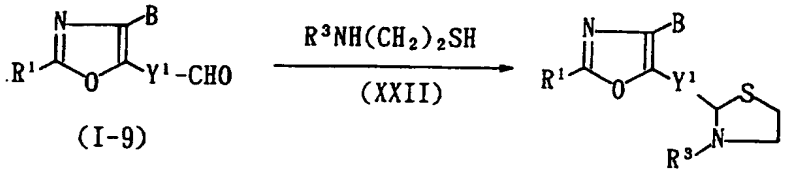


wherein all symbols are of the same meanings as those mentioned above.

In this method, the compound(XIX) can be produced by condensing the compound(XVII) and the compound(XVIII). This condensing reaction is the same manner as producing the compound(VII) by condensing the compound(V) and the compound(VI) as described in the Method R. Further, the compound(XX) can be produced by halogenating the compound(XIX). This halogenating reaction is the same manner as the halogenating reaction of the compound(II) as described in the Method A. The compound(XXI) can be produced by reacting with

thus-obtained compound(XX) and the compound(XI). This reaction is conducted in the same manner as producing the compound(I-5) by reacting with the compound(I-4) and the compound(XI). Further, the compound(XVI) can be produced by reducing the compound(XXI). The reducting reaction is conducted in the same manner as the reacting reaction as described in the Method E.

Method O:



(I-9) (I-17)

wherein all symbols are of the same meanings as those mentioned above.

The compound(I-17) wherein A is a heterocyclic group in the compound(I) can be produced by reacting with the compound(I-9) and the compound(XXII). This reaction may be effected in any ordinary manner, for example, in the presence of a base or an acid in a solvent that does not have any influence on the reaction. The acid used in this reaction includes, for example, hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid and p-toluenesulfonic acid. The base used in this reaction includes, for example, sodium acetate and p-toluenesulfonyl pyridine.

The amount of the acid or the base to be used may be from about 0.1 to 2 molar equivalents relative to the compound(I-9).

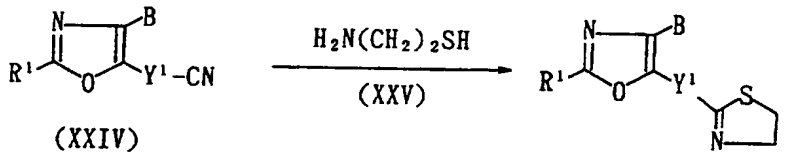
The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene; tetrahydrofuran; acetic acid.

The reaction temperature generally ranges from

about -20 to 200°C, preferably from about 0 to 150°C. The reaction time ranges from about 0.5 to 20 hours.

The compounds (I-17) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extration, precipitation, recrystallization, phasic transfer, chromatography or the like.

Method P:



(XXIV)

(I-18)

wherein all symbols are of the same meanings as those mentioned above.

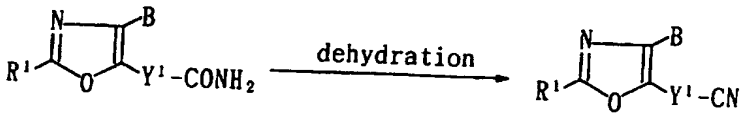
The compound(I-18) wherein A is a heterocyclic group in the compound(I) can be produced by reacting with the compound(XXIV) anad the compound(XXV). This reaction may be conducted in any ordinary manner in a solvent that does not have any influence on the reaction. The solvent that does not have any influence on the reaction includes, for example, alcohols such as methanol, ethanol, propanol, isopropanol; aromatic hydrocarbons such as benzene, toluene; tetrahydrofuran; N,N-dimethylformamide; pyridine; acetic acid.

The reaction temperature generally ranges from about -20 to 200°C, preferably about 0 to 150°C. The reaction time ranges from about 0.5 to 20 hours.

The compounds (I-18) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extration, precipitation, recrystallization, phasic transfer,

chromatography or the like.

Method O:



(I-19) (XXIV)

wherein all symbols are of the same meanings as those mentioned above.

The compound(XXIV) can be produced by dehydration of the compound(I-19). This reaction may be conducted in any ordinary manner in a solvent that does not have any influences on the reaction. The dehydrating agent includes, for example, sulfuric acid, acetic anhydride, phosphorus pentaoxide, phosphorus oxychloride. This solvent that does not have any influences on the reaction includes, for example, alcohols such as methanol, ethanol, propanol, isopropanol; aromatic hydrocarbons such as benzene, toluene; tetrahydrofuran; N,N-dimethylformamide.

The reaction temperature generally ranges from about -20 to 200°C, preferably 0 to 150°C. The reaction time ranges from about 0.5 to 20 hours.

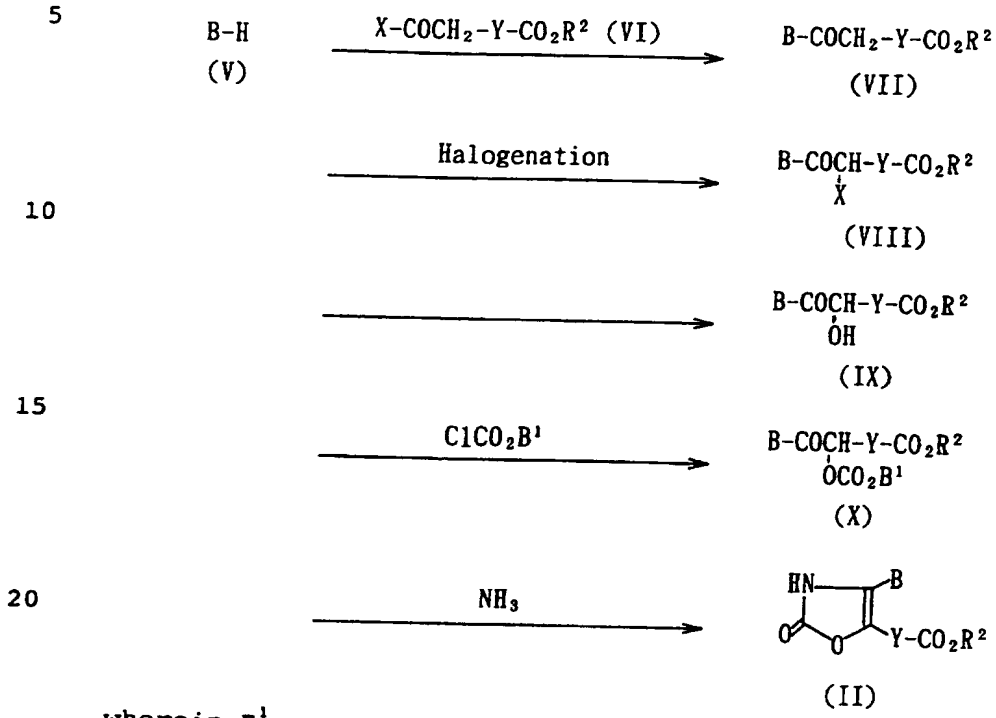
The compounds (XXIV) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extration, precipitation, recrystallization, phasic transfer, chromatography or the like.

The starting compounds (II), (III) and (IV) to be used for the production of the compounds (I) of the invention can be produced by any per-se known methods. For example, these starting compounds can be produced by the methods mentioned hereinafter or according to these, or by the methods described in EP-92239 and

JP59-190976 or according to those methods.

The starting compounds (II) for the Method A can be produced, for example, by the following method R.

Method R:



wherein B^1 represents an optionally substituted phenyl group; and the other symbols are of the same meanings as those mentioned above.

The substituent for the optionally substituted phenyl group represented by B^1 includes, for example, an alkyl group having 1 to 4 carbon atoms (e.g., methyl), a halogen atom (e.g., chlorine), and a nitro group.

In this process, a compound (V) is first condensed with a compound (VI) to obtain a compound (VII). This reaction may be conducted in any ordinary manner, in the presence of a Lewis acid and in the presence of a solvent that does not have any influence on the reaction or in the presence of no solvent.

The Lewis acid includes, for example, aluminium chloride, titanium tetrachloride, tin tetrachloride, and boron trifluoride. The amount of the Lewis acid to be used may be preferably from 1 to 5 molar equivalents relative to the compound (V).

The solvent that does not any influence on the reaction includes, for example, halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and carbon tetrachloride; carbon disulfide; and mixed solvents of these.

The amount of the compound (VI) to be used may be from 1 to 5 molar equivalents, preferably from 1 to 3 molar equivalents, relative to the compound (V).

The reaction temperature ranges generally from -20°C to 150°C, preferably from about -10°C to about 80°C. The reaction time ranges from 0.5 to 20 hours.

Next, the compound (VII) is halogenated to obtain a compound (VIII). This reaction may be conducted in any ordinary manner, generally in the presence of a halogenating agent in a solvent that does not have any influence on the reaction.

The halogenating agent includes, for example, chlorine and bromine. The amount of the halogenating agent to be used may be preferably from 1 to 1.5 molar equivalents relative to the compound (VII).

The solvent that does not have any influence on the reaction includes, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; halogenated hydrocarbons such as dichloromethane and chloroform; acetic acid; and mixed solvents of these.

The reaction temperature ranges generally from -20°C to 150°C, preferably from about -10°C to about 80°C. The reaction time ranges from 0.5 to 20 hours.

Next, the thus-obtained compound (VIII) is suitably reacted with a salt of an organic acid in the presence of a solvent that does not have any influence

(40 ml) was added to the reaction mixture, and stirred under reflux for an additional 30 minutes. Water was added to the reaction mixture, which was then neutralized with 6 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 3-[4-(4-chlorophenyl)-2-thioxo-4-oxazolin-5-yl]propionic acid (5.41 g, yield: 96 %). This was recrystallized from ethanol to give colorless needles. mp 196-197°C.

Reference Example 5:

Phosphorus oxychloride(585mg) was added dropwise into a N,N-dimethylformamide solution (20ml) of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionamide(840mg) at room temperature. After stirring for 1 hour, the reaction mixture was poured into ice water, and neutralized with saturated sodium bicarbonate. The precipitating crystals are collected by filtration to give 4-(4-chlorophenyl)-5-(2-cyanoethyl)-2-(2-methyl-1-imidazolyl)oxazole(650mg, 82%). This was recrystallized with acetone-isopropyl ether to give colorless prisms. mp 163-164°C

Reference Example 6:

Adipic acid monomethyl ester chloride (17.9g) was added dropwise into a mixture of chlorobenzene(33.8g) and aluminum chloride anhydrous(26.7g) with cooling with ice. After stirring for 2 hours, the reaction mixture was poured into ice water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The solvent was evaporated to give methyl 5-(4-chlorobenzoyl)pentanoate. This was dissolved into dichloromethane(100ml), thereto bromine(16.0g) was added dropwise. The reaction mixture was washed with water and then with sodium hydrogensulfite. The dichloromethane layer was washed

with water, and dried ($MgSO_4$). The solvent was evaporated to give methyl 5-bromo-5-(4-chlorobenzoyl)pentanoate(31.7g, 95%) as an oily substance.

NMR(δ ppm in $CDCl_3$): 1.6-2.3(4H, m), 2.42(2H, t, J=7Hz), 3.68(3H, s), 5.08(1H, dd, J=8&6.5Hz), 7.47(2H, d, J=9Hz), 7.96(2H, d, J=9Hz).

Reference Example 7:

In the same manner as Reference Example 2, methyl 5-(4-chlorobenzoyl)-5-phenoxycarbonyloxypentanoate as an oily substance (yield: 67%) was obtained by reacting a reactant which was obtained by reacting methyl 5-bromo-5-(4-chlorobenzoyl)pentanoate with sodium formate, with phenyl chlorocarbonate.

NMR(δ ppm in $CDCl_3$): 1.8-2.1(4H, m), 2.40(2H, t, J=7Hz), 3.67(3H, s), 5.82(1H, dd, J=7.5&4.5Hz), 7.15-7.45(5H, m), 7.48(2H, d, J=9Hz), 7.91(2H, d, J=9Hz).

Reference Example 8:

In the same manner as Reference Example 3, obtained was methyl 4-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]butanoate by reaction of methyl 5-(4-chlorobenzoyl)-5-phenoxycarbonyloxypentanoate with ammonium acetate. This was recrystallized with acetone-isopropyl ether to give colorless prisms. mp 121-122°C

Reference Example 9:

Titanium tetrachloride(15.5g) was added dropwise into a mixture of 4-(4-chlorophenyl)-4-oxazolin-2-one(4.00g), ethyl chloroglyoxylate(5.58g) and dichloromethane(30ml) at room temperature. After stirring for 2 hours, the reaction mixture was poured into ice water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and

dried($MgSO_4$). The solvent was evaporated to give ethyl 2-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]-2-oxoacetate as crystals(5.38g, 89%). This was recrystallized from ethyl acetate-hexane to give pale yellow prisms. mp 152-153°C

Reference Example 10:

A mixture of ethyl 2-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]-2-oxoacetate(2.50g), phosphorus oxychloride(6.48g) and pyridine(740mg) was stirred for 1 hour at 120-125°C. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane(1:9, v/v), obtained was ethyl 2-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-2-oxoacetate(450 mg, 17%). This was recrystallized from ethyl acetate-hexane to give colorless prisms. mp 98-99°C

Reference Example 11:

Sodium hydride(oil, 60%, 710mg) was gradually added to a mixture of ethyl 2-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]-2-oxoacetate(4.63g), 2-methylimidazole(1.45g) and N,N-dimethylformamide(50ml) at 0°C. After stirring for 1 hour at room temperature, the reaction mixture was poured into ice water to give ethyl 2-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-2-oxoacetate(3.12g, 59%). This was recrystallized from ethyl acetate-hexane to give colorless prisms. mp 126-127°C

Reference Example 12:

Sodium borohydride(95mg) was added to a tetrahydrofuran(60ml)-2-propanol(30ml) solution of

ethyl 2-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-2-oxoacetate(2.93g) at 0°C. After stirring for 30 minutes, the reaction mixture was poured into ice water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The solvent was evaporated to give ethyl 2-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-2-hydroxyacetate(2.20g, 75%). This was recrystallized from acetone-ethyl acetate to give colorless prisms.
mp 197-198°C (degradation)

Reference Example 13:

N,N-dimethylformamide(1 drop) was added to a tetrahydrofuran solution(40ml) of pimelic acid monoethyl ester(25.5g), and thereto oxalyl chloride(18.8g) was added dropwise. After stirring for 2 hours at room temperature, the reaction mixture was concentrated. The residue was added dropwise to a mixture of chlorobenzene(61.0g) and aluminum chloride anhydrous (36.1g) under ice water. After stirring for 3 hours, the reaction mixture was poured into 1N-hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The solvent was evaporated to give ethyl 6-(4-chlorobenzoyl)hexanate (37.7g, 97%) as an oily substance.
NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.3-1.9(6H, m), 2.32(2H, t, J=7.5Hz), 2.95(2H, t, J=7.5Hz), 4.13(2H, q, J=7Hz), 7.44(2H, d, J=8.5Hz), 7.90(2H, d, J=8.5Hz).

Reference Example 14:

In the same manner as Reference Example 13, obtained was ethyl 7-(4-chlorobenzoyl)heptanoate as an oily substance(yield: 90%) by reaction of a reactant of suberic acid monoethyl ester and oxalyl chloride, with

chlorobenzene.
NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.2-1.9(8H, m), 2.2-2.4(2H, m), 2.93(2H, t, J=7.5Hz), 4.13(2H, q, J=7Hz), 7.43(2H, d, J=8.5Hz), 7.90(2H, d, J=8.5Hz).

Reference Example 15:

Bromine(21.1g) was added dropwise to a dichloromethane solution (200ml) of ethyl 6-(4-chlorobenzoyl)hexanoate (37.3g) at room temperature. After stirring for 30 minutes, the reaction mixture was washed with sodium hydrogensulfite, saturated sodium bicarbonate and water in turn. The dichloromethane layer was dried($MgSO_4$). The solvent was evaporated to give ethyl 6-bromo-6-(4-chlorobenzoyl)hexanoate(47.6g, quant.) as an oily substance.
NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.3-2.3(6H, m), 2.34(2H, t, J=7Hz), 4.13(2H, q, J=7Hz), 5.06(1H, t, J=7Hz), 7.47(2H, d, J=8.5Hz), 7.96(2H, d, J=8.5Hz).

Reference Example 16:

In the same manner as Reference Example 15, obtained was ethyl 7-bromo-7-(4-chlorobenzoyl)heptanoate(yield: 79%) as an oily substance through reaction of ethyl 7-(4-chlorobenzoyl)heptanoate with bromine.
NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.2-1.9(8H, m), 2.2-2.4(2H, m), 4.12(2H, q, J=7Hz), 5.06(1H, t, J=7Hz), 7.47(2H, d, J=8.5Hz), 7.96(2H, d, J=8.5Hz).

Reference Example 17:

A mixture of ethyl 6-bromo-6-(4-chlorobenzoyl)hexanoate (47.6g), sodium formate(44.8g) and methanol(250ml) was stirred for 24 hours under reflux. The reaction mixture was concentrated. Water was added to the reaction mixture. This was extracted with ethyl acetate. The ethyl acetate layer was washed

with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane(1:4, v/v), obtained was ethyl 6-(4-chlorobenzoyl)-6-hydroxyhexanoate(24.5g, 62%) as an oily substance.

NMR(δ ppm in $CDCl_3$): 1.23(3H, t, J=7Hz), 1.3-2.0(6H, m), 2.28(2H, t, J=7Hz), 3.63(1H, d, J=6.5Hz), 4.10(2H, q, J=7Hz), 4.95-5.1(1H, m), 7.49(2H, d, J=8.5Hz), 7.86(2H, d, J=8.5Hz).

Reference Example 18:

In the same manner as Reference Example 17, obtained was ethyl 7-(4-chlorobenzoyl)-7-hydroxyheptanoate (yield: 31%) as an oily substance by reaction of ethyl 7-bromo-7-(4-chlorobenzoyl)heptanoate with sodium formate in methanol.

NMR(δ ppm in $CDCl_3$): 1.24(3H, t, J=7Hz), 1.3-2.0(8H, m), 2.27(2H, t, J=7.5Hz), 3.63(1H, d, J=6.5Hz), 4.11(2H, q, J=7Hz), 4.95-5.1(1H, m), 7.49(2H, d, J=8.5Hz), 7.87(2H, d, J=8.5Hz).

Reference Example 19:

Phenyl chloroformate (14.1g) was added dropwise to a mixture of ethyl 6-(4-chlorobenzoyl)-6-hydroxyhexanoate (24.5g), pyridine(7.14g) and tetrahydrofuran(200ml) with cooling with ice. After stirring for 3 hours at room temperature, the reaction mixture was poured into ice water, and neutrized by 2N-hydrochloric acid. This was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The solvent was evaporated to give ethyl 6-(4-chlorobenzoyl)-6-phenoxycarbonyloxyhexanate(32.3g, 94%) as an oily substance.

NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.45-2.05(6H,

m), 2.32(2H, t, J=7Hz), 4.12(2H, q, J=7Hz), 5.79(1H, t, J=6Hz), 7.1-7.5(7H, m), 7.89(2H, d, J=8.5Hz).

Reference Example 20:

In the same manner as Reference Example 19, obtained was ethyl 7-(4-chlorobenzoyl)-7-phenoxycarbonyloxyheptanoate (quant.) as an oily substance by reaction of ethyl 7-(4-chlorobenzoyl)-7-hydroxyheptanoate with phenyl chloroformate.
NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.25-2.0(8H, m), 2.29(2H, t, J=7.5Hz), 4.12(2H, q, J=7Hz), 5.79(1H, t, J=7Hz), 7.15-7.45(5H, m), 7.48(2H, d, J=8.5Hz), 7.90(2H, d, J=8.5Hz).

Reference Example 21:

Ethyl 6-(4-chlorobenzoyl)-6-phenoxycarbonyloxyhexanoate (32.3g), ammonium acetate(29.7g) and acetic acid(150ml) was stirred for 1 hour under reflux. Water was added to the reaction mixture to give ethyl 5-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]pentanoate(17.7g, 71%). This was recrystallized from acetone-isopropyl ether to give colorless needls. mp 143-144°C

Reference Example 22:

In the same manner as Reference Example 21, obtained was ethyl 6-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]hexanoate (yield: 87%) by reaction of ethyl 7-(4-chlorobenzoyl)-7-phenoxycarbonyloxyheptanoate with ammonium acetate. This was recrystallized with acetone-isopropyl ether to give colorless prisms. mp 113-114°C

Example 1:

A mixture of methyl 3-[4-(4-chlorophenyl)-2-oxo-4-oxazoline-5-yl]propionate (11.3 g), phosphorus

oxychloride (18.6 g) and pyridine (3.2 ml) was stirred at 120 to 180°C for 80 minutes. The reaction mixture was concentrated, and ice water was added thereto and then stirred at room temperature for 30 minutes. Then, this was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The solvent was evaporated, and the crystals thus precipitated were collected by filtration. These were recrystallized from isopropyl ether to give colorless needles of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate (8.56 g, 71 %). m.p. 71-72°C.

Example 2:

An aqueous solution of 1 N sodium hydroxide (34 ml) was dropwise added to an ethanol (50 ml) solution of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate (8.50 g), with cooling with ice. After stirring for 20 minutes with cooling and then for 30 minutes at room temperature, 2 N hydrochloric acid was added thereto, and the crystals thus precipitated were collected by filtration to obtain 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (8.00 g, 99 %). This was recrystallized from ethyl acetate to give colorless prisms. mp 169-170°C.

Example 3:

2-Chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g) was added to an ethanol solution of sodium ethoxide prepared from sodium (0.35 g) and ethanol (15 ml), and stirred under reflux for 30 minutes. The solvent was evaporated, and water was added to the residue, which was then acidified with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-ethoxy-5-oxazolepropionic acid (1.40 g, 95 %). This was recrystallized from ethanol to give colorless

prisms. mp 148-149°C.

Example 4:

Sodium hydride (60 % dispersion in oil, 0.60 g) was added to 2-propanol (20 ml), and stirred at room temperature for 10 minutes. To the reaction mixture was added 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), and stirred under reflux for 30 minutes. Next, water was added to the resulting reaction mixture, which was then acidified with 2 N hydrochloric acid, and the crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-isopropoxy-5-oxazolepropionic acid (1.35 g, 87 %). This was recrystallized from isopropyl ether to give colorless prisms. mp 116-117°C.

Example 5:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), phenol (0.94 g), potassium carbonate (2.10 g) and N,N-dimethylformamide (10 ml) was stirred at 140°C for 3 hours. Water was added to the reaction mixture, which was then acidified with 6 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-phenoxy-5-oxazolepropionic acid (1.60 g, 93 %). This was recrystallized from ethyl acetate to give colorless needles. mp 136-137°C.

Example 6:

Methyl iodide (0.34 ml) was dropwise added to a mixture of 3-[4-(4-chlorophenyl)-2-thioxo-4-oxazolin-5-yl]propionic acid (1.42 g), an aqueous solution of 2 N sodium hydroxide (5.5 ml) and N,N-dimethylformamide (15 ml), with cooling with ice. After the reaction mixture was stirred for 30 minutes, water was added to the resulting reaction mixture, which was then acidified

with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-methylthio-5-oxazolepropionic acid (1.45 g, 97 %). This was recrystallized from ethanol to give colorless needles. mp 183-184°C.

Example 7:

In the same manner as in Example 6, obtained was 4-(4-chlorophenyl)-2-isopropylthio-5-oxazolepropionic acid (yield: 80 %) by reaction of 3-[4-(4-chlorophenyl)-2-thioxo-4-oxazolin-5-yl]propionic acid with isopropyl iodide. This was recrystallized from ethanol to give colorless prisms. mp 132-133°C.

Example 8:

In the same manner as in Example 6, obtained was 4-(4-chlorophenyl)-2-(2-pyridylmethylthio)-5-oxazolepropionic acid (yield: 98 %) by reaction of 3-[4-(4-chlorophenyl)-2-thioxo-4-oxazolin-5-yl]propionic acid with 2-(chloromethyl)pyridine. This was recrystallized from ethanol to give colorless prisms. mp 125-126°C.

Example 9:

In the same manner as in Example 6, obtained was 4-(4-chlorophenyl)-2-(3-pyridylmethylthio)-5-oxazolepropionic acid (yield: 96 %) by reaction of 3-[4-(4-chlorophenyl)-2-thioxo-4-oxazolin-5-yl]propionic acid with 3-(chloromethyl)pyridine. This was recrystallized from ethanol to give colorless needles. mp 129-130°C.

Example 10:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), thiophenol (0.54 ml), sodium methoxide-methanol solution (28 %, 2.00 g) and

methanol (15 ml) was stirred under reflux for 16 hours. Water was added to the reaction mixture, which was then acidified with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-phenylthio-5-oxazolepropionic acid (1.60 g, 89 %). This was recrystallized from methanol to give colorless needles. mp 156-157°C.

Example 11:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), 4-methylthiophenol (0.68 g), potassium carbonate (2.07 g) and N,N-dimethylformamide (20 ml) was stirred under a nitrogen atmosphere at 100°C for 40 minutes. Water was added to the reaction mixture, which was then acidified with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-(4-methylphenylthio)-5-oxazolepropionic acid (1.73 g, 93 %). This was recrystallized from ethanol to give colorless needles. mp 160-161°C.

Example 12:

In the same manner as in Example 11, obtained was 4-(4-chlorophenyl)-2-(4-methyl-4H-1,2,4-triazol-3-ylthio)-5-oxazolepropionic acid (yield: 77 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 4-methyl-4H-1,2,4-triazole-3-thiol. This was recrystallized from ethanol to give pale brown needles. mp 186-188°C.

Example 13:

In the same manner as in Example 11, obtained was 4-(4-chlorophenyl)-2-(4-phenyl-4H-1,2,4-triazol-3-ylthio)-5-oxazolepropionic acid (yield: 61 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-

oxazolepropionic acid with 4-phenyl-4H-1,2,4-triazole-3-thiol. This was recrystallized from ethanol to give colorless needles. mp 122-123°C.

Example 14:

In the same manner as in Example 11, obtained was 4-(4-chlorophenyl)-2-(1-phenyl-2-imidazolylthio)-5-oxazolepropionic acid (yield: 39 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 1-phenylimidazole-2-thiol. This was recrystallized from ethanol to give pale brown needles. mp 185-187°C.

Example 15:

In the same manner as in Example 11, obtained was 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionic acid (yield: 95 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 2-mercaptopyridine. This was recrystallized from ethanol to give pale yellow needles. mp 172-173°C.

Example 16:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), an aqueous solution of 30 % methylamine (4.0 ml) and 2-propanol (20 ml) was stirred in a sealed tube at 100°C for 4 hours. The reaction mixture was concentrated, and water was added to the resulting residue. The pH was then adjusted 3 with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-methylamino-5-oxazolepropionic acid (1.21 g, 86 %). This was recrystallized from ethanol to give colorless prisms. mp 217-218°C.

Example 17:

In the same manner as in Example 16, obtained was 4-(4-chlorophenyl)-2-dimethylamino-5-oxazolepropionic

acid (yield: 92 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with dimethylamine. This was recrystallized from ethanol to give colorless needles. mp 189-190°C.

Example 18:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), morpholine (2.2 ml) and 2-propanol (20 ml) was stirred under reflux for 4 hours. The reaction mixture was concentrated, and water was added to the residue. The pH was then adjusted 3 with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-morpholino-5-oxazolepropionic acid (1.64 g, 98 %). This was recrystallized from ethanol to give colorless needles. mp 180-181°C.

Example 19:

In the same manner as in Example 18, obtained was 4-(4-chlorophenyl)-2-cyclohexylamino-5-oxazolepropionic acid (yield: 53 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with cyclohexylamine. This was recrystallized from ethanol to give colorless needles. mp 237-238°C.

Example 20:

In the same manner as in Example 18, obtained was 4-(4-chlorophenyl)-2-(1-pyrrolidinyl)-5-oxazolepropionic acid (yield: 99 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with pyrrolidine. This was recrystallized from ethanol to give colorless needles. mp 199-200°C.

Example 21:

In the same manner as in Example 18, obtained was

4-(4-chlorophenyl)-2-piperidino-5-oxazolepropionic acid (yield: 97 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with piperidine. This was recrystallized from ethanol to give colorless prisms. mp 185-186°C.

Example 22:

In the same manner as in Example 18, obtained was 4-(4-chlorophenyl)-2-(2-methylpiperidino)-5-oxazolepropionic acid (yield: 44 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 2-methylpiperidine. This was recrystallized from isopropyl ether to give colorless prisms. mp 126-128°C.

Example 23:

In the same manner as in Example 18, obtained was 4-(4-chlorophenyl)-2-hexamethyleneimino-5-oxazolepropionic acid (yield: 90 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with hexamethyleneimine. This was recrystallized from ethanol to give colorless prisms. mp 137-138°C.

Example 24:

A mixture of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid (1.43 g), imidazole (1.70 g), potassium carbonate (2.80 g) and N,N-dimethylformamide (15 ml) was stirred at 130°C for 2.5 hours. Water was added to the reaction mixture. The pH was then adjusted 6 with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionic acid (1.35 g, 85 %). This was recrystallized from methanol to give colorless needles. mp 194-195°C.

Example 25:

In the same manner as in Example 24, obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid (yield: 54 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 2-methylimidazole. This was recrystallized from methanol to give colorless needles. mp 195-197°C.

Example 26:

In the same manner as in Example 24, obtained was 4-(4-chlorophenyl)-2-(2-ethyl-1-imidazolyl)-5-oxazolepropionic acid (yield: 88 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 2-ethylimidazole. This was recrystallized from methanol to give colorless needles. mp 197-199°C.

Example 27:

In the same manner as in Example 24, obtained was 4-(4-chlorophenyl)-2-(2-phenyl-1-imidazolyl)-5-oxazolepropionic acid (yield: 29 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 2-phenylimidazole. This was recrystallized from ethanol to give colorless needles. mp 179-180°C.

Example 28:

In the same manner as in Example 24, obtained was 4-(4-chlorophenyl)-2-(1-pyrazolyl)-5-oxazolepropionic acid (yield: 91 %) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with pyrazole. This was recrystallized from methanol to give colorless needles. mp 171-172°C.

Example 29:

In the same manner as in Example 24, obtained was 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionic acid (yield: 91 %) by reaction of 2-

chloro-4-(4-chlorophenyl)-5-oxazolepropionic acid with 1,2,4-triazole. This was recrystallized from ethanol to give colorless prisms. m.p. 168-169°C.

Example 30:

Methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate (1.50 g) and 2-propylimidazole (0.66 g) were dissolved in N,N-dimethylformamide (10 ml), and sodium hydride (60 % dispersion in oil, 0.30 g) was gradually added to the resulting solution at room temperature. After this was stirred at room temperature for 3.5 hours, an aqueous solution of 2 N sodium hydroxide (50 ml) was added thereto and stirred for an additional 30 minutes. Water was added to the reaction mixture, and the pH was then adjusted to 6 with 2 N hydrochloric acid. The crystals thus precipitated were collected by filtration, and recrystallized from ethanol to obtain 4-(4-chlorophenyl)-2-(2-propyl-1-imidazolyl)-5-oxazolepropionic acid (1.25 g, 69 %) as pale brown needles. mp 174-175°C.

Example 31:

In the same manner as in Example 30, obtained was 4-(4-chlorophenyl)-2-(2-isopropyl-1-imidazolyl)-5-oxazolepropionic acid (yield: 59 %) by reaction of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate with 2-isopropylimidazole followed by hydrolysis of the resulting product. This was recrystallized from ethyl acetate to give colorless prisms. mp 173-174°C.

Example 32:

In the same manner as in Example 30, obtained was 4-(4-chlorophenyl)-2-(2-methylthio-1-imidazolyl)-5-oxazolep ropionic acid (yield: 87 %) by reaction of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate

with 2-methylthioimidazole followed by hydrolysis of the resulting product. This was recrystallized from chloroform-ethanol to give colorless needles. mp 225-226°C.

Example 33:

In the same manner as in Example 30, obtained was 4-(4-chlorophenyl)-2-(4,5-dimethyl-1-imidazolyl)-5-oxazolepropionic acid (yield: 77 %) by reaction of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate with 4,5-dimethylimidazole followed by hydrolysis of the resulting product. This was recrystallized from chloroform-methanol to give pale brown needles. mp 225-226°C.

Example 34:

In the same manner as in Example 30, obtained was 4-(4-chlorophenyl)-2-(1-benzimidazolyl)-5-oxazolepropionic acid (yield: 82 %) by reaction of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate with benzimidazole followed by hydrolysis of the resulting product. This was recrystallized from chloroform-methanol to give pale brown prisms. mp 217-218°C.

Example 35:

In the same manner as in Example 30, obtained was 4-(4-chlorophenyl)-2-(3,5-dimethyl-1-pyrazolyl)-5-oxazolepropionic acid (yield: 90 %) by reaction of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate with 3,5-dimethylpyrazole followed by hydrolysis of the resulting product. This was recrystallized from ethanol to give colorless needles. mp 201-202°C.

Example 36:

Lithium aluminium hydride (185 mg) was gradually

added to a tetrahydrofuran (20 ml) solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid (1.47 g) at room temperature. After the mixture was stirred for 1 hour, water (2 ml) was added to the reaction mixture with cooling with ice, and stirred for further 30 minutes. Diethyl ether (50 ml) was added to the reaction mixture, which was then dried ($MgSO_4$), and the insoluble substances were removed by filtration. The resulting filtrate was concentrated, and the crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol (435 mg, 31 %). This was recrystallized from dichloromethane-isopropyl ether to give colorless prisms. mp 128-129°C.

Example 37:

In the same manner as in Example 36, obtained was 4-(4-chlorophenyl)-2-(1-pyrazolyl)-5-oxazolepropanol (yield: 33 %) by reduction of 4-(4-chlorophenyl)-2-(1-pyrazolyl)-5-oxazolepropionic acid with lithium aluminium hydride. This was recrystallized from diethyl ether-hexane to give colorless prisms. mp 75-76°C.

Example 38:

A toluene solution of diethyl azodicarboxylate (40 %, 880 mg) was dropwise added to a tetrahydrofuran (10 ml) solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol (320 mg), 1,2,4-triazole (140 mg) and tributylphosphine (410 mg) at room temperature. After stirring for 1 hour, the reaction mixture was concentrated, and the residue was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (2:1, v/v), obtained was 1-[3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-

oxazolyl]propyl]-1,2,4-triazole (305 mg, 82 %). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 142-143°C.

Example 39:

In the same manner as in Example 38, obtained was 4-(4-chlorophenyl)-5-[3-(2-methoxyphenoxy)propyl]-2-(2-methyl-1-imidazolyl)oxazole (yield: 54 %) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol with 2-methoxyphenol. This was recrystallized from diethyl ether-hexane to give colorless needles. mp 84-85°C.

Example 40:

In the same manner as in Example 38, obtained was 3-[3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl]-1-methylhydantoin (yield: 77 %) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol with 1-methylhydantoin. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 105-106°C.

Example 41:

Ethyl chloroformate (395 mg) was dropwise added to a tetrahydrofuran (40 ml) solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid (1.00 g) and triethylamine (365 mg), at -30°C. After stirring for 40 minutes, the reaction mixture was added to a mixture of aqueous ammonia (28 %, 30 ml) and tetrahydrofuran (10 ml) at 0°C, and then stirred at room temperature for 1 hour. Water was added to the reaction mixture, and the crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionamide (900 mg, 90 %). This was recrystallized from methanol-ethyl acetate to give

colorless needles. mp 215-216°C.

Example 42:

Ethyl chloroformate (590 mg) was dropwise added to a tetrahydrofuran (40 ml) solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid (1.50 g) and triethylamine (550 mg), at -30°C. After stirring for 30 minutes, the reaction mixture was poured into a solution as prepared from 2-chloroethylamine hydrochloride (2.62 g), triethylamine (2.29 g) and N,N-dimethylformamide (20 ml), at 0°C, and then stirred at room temperature for 1 hour. The reaction mixture was poured into water, and the crystals thus precipitated were collected by filtration to obtain N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionamide (1.53 g, 86 %). This was recrystallized from ethyl acetate-hexane to give colorless needles. mp 155-156°C.

Example 43:

In the same manner as in Example 42, obtained was N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionamide (yield: 77 %) from 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionic acid. This was recrystallized from acetone-isopropyl ether to give colorless needles. mp 130-131°C.

Example 44:

In the same manner as in Example 42, obtained was N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionamide (yield: 87 %) from 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionic acid. This was recrystallized from ethyl acetate-isopropyl ether to give colorless needles. mp 157-158°C.

Example 45:

Ethyl chloroformate (435 mg) was dropwise added to a tetrahydrofuran (30 ml) solution of 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionic acid (1.20 g) and triethylamine (405 mg), at -30°C. After stirring for 30 minutes, the reaction mixture was poured into a solution as prepared from 2-chloroethylamine hydrochloride (1.93 g), triethylamine (1.68 g) and N,N-dimethylformamide (20 ml), at 0°C, and stirred at room temperature for 1 hour. The reaction mixture was poured into water, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$), and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (1:2, v/v), obtained was N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionamide (1.29 g, 91%) as an oily substance. NMR (δ ppm in $CDCl_3$): 2.65(2H,t,J=7.5Hz), 3.29(2H,t,J=7.5Hz), 3.4-3.6(4H,m), 6.24(1H,brs), 7.21(1H,ddd,J=7.5&5&1Hz), 7.35-7.5(3H,m), 7.6-7.75(3H,m), 8.49(1H,dd,J=5&1Hz).

Example 46:

Sodium hydride (60 % dispersion in oil, 265 mg) was gradually added to a solution of N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionamide (1.30 g) in N,N-dimethylformamide (30 ml), at room temperature. After stirring at room temperature for 3 hours, the reaction mixture was poured into ice water, and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$), and the solvent was evaporated. The crystals thus precipitated were collected by filtration to obtain 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[2-(2-oxazolin-2-

yl)ethyl]oxazole (1.07 g, 91 %). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 119-120°C.

Example 47:

In the same manner as in Example 46, obtained was 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-[2-(2-oxazolin-2-yl)ethyl]oxazole (yield: 69 %) by cyclization of N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionamide. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 120-121°C.

Example 48:

In the same manner as in Example 46, obtained was 1-[4-(4-chlorophenyl)-5-[2-(2-oxazolin-2-yl)ethyl]-2-oxazolyl]-1,2,4-triazole (yield: 85 %) by cyclization of N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionamide. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 132-133°C.

Example 49:

In the same manner as in Example 46, N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionamide was cyclized, the reaction mixture was poured into water, and extracted, the resulting extract was washed with water and dried ($MgSO_4$), the solvent was evaporated, and the resulting residue was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (1:2, v/v), obtained was 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-[2-(2-oxazolin-2-yl)ethyl]oxazole as an oily substance (yield: 67 %). NMR (δ ppm in $CDCl_3$): 2.65-2.8(2H,m), 3.2-3.35(2H,m), 3.80(2H,t,J=9.5Hz), 4.21(2H,t,J=9.5Hz), 7.16(1H,ddd,J=7.5&5&1Hz), 7.35-7.45(3H,m), 7.55-

7.7(3H,m), 8.4(1H,ddd,J=5&2&0.5Hz).

Example 50:

Ethyl chloroformate (450 mg) was dropwise added to a tetrahydrofuran (40 ml) solution of 4-(4-chlorophenyl)-2-(2-ethyl-1-imidazolyl)-5-oxazolepropionic acid (1.20 g) and triethylamine (420 mg), at -30°C. After stirring for 1 hour, the reaction mixture was poured into a solution as prepared from 2-chloroethylamine hydrochloride (2.01 g), triethylamine (1.76 g) and tetrahydrofuran (40 ml), at 0°C, and stirred at room temperature for 1.5 hours. The reaction mixture was poured into water and then extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried (with $MgSO_4$), and the solvent was evaporated. The crystals (910 mg) thus precipitated were collected by filtration. The crystals were stirred along with potassium carbonate (370 mg) in N,N-dimethylformamide (20 ml) at 90 to 100°C for 1.5 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$), and the solvent was evaporated. The resulting residue was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (2:3, v/v), obtained was 4-(4-chlorophenyl)-2-(2-ethyl-1-imidazolyl)-5-[2-(2-oxazolin-2-yl)ethyl]oxazole (320 mg, 25 %). This was recrystallized from isopropyl ether to give colorless prisms. mp 53-54°C.

Example 51:

In the same manner as in Example 50, obtained was 4-(4-chlorophenyl)-5-[2-(2-oxazolin-2-yl)ethyl]-2-(1-pyrazolyl)oxazole (yield: 42 %) by reaction of 4-(4-chlorophenyl)-2-(1-pyrazolyl)-5-oxazolepropionic acid

with 2-chloroethylamine followed by cyclization of the resulting product. This was recrystallized from acetone-isopropyl ether to give colorless needles. mp 79-80°C.

Example 52:

A mixture of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid(500mg), potassium carbonate(310mg), iodoethane(350mg) and N,N-dimethylformamide(10ml) was stirred at room temperature for 16 hours. Water was added to the mixture, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The solvent was evaporated and the crystals thus precipitated were collected by filtration. These were recrystallized from acetone-hexane to give colorless of ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionate(495mg, 91%). mp 70-71°C

Example 53:

In the same manner as Example 52, obtained was benzyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazole propionate (yield: 88%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid with benzyl bromide. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 71-72°C

Example 54:

In the same manner as Example 52, obtained was ethyl 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionate (yield: 92%) by reaction of 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionic acid with iodoethane. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 67-68°C

Example 55:

In the same manner as Example 52, obtained was ethyl 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionate (yield: 93%) by reaction of 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionic acid with iodoethane. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 99-100°C

Example 56:

Water was added to a mixture which was obtained by reacting 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionic acid with iodoethane in the same manner as Example 52. This was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The residue obtained by evaporated the solvent was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane (1:4, v/v), obtained was ethyl 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionate(yield: 96%) as an oily substance. NMR(δ ppm in $CDCl_3$): 1.22(3H, t, J=7Hz), 2.74(2H, t, J=7.5Hz), 3.25(2H, t, J=7.5Hz), 4.12(2H, q, J=7Hz), 7.16(1H, ddd, J=7.5&5&1Hz), 7.35-7.45(3H, m), 7.55-7.7(3H, m), 8.48(1H, ddd, J=5&2&1Hz).

Example 57:

Lithium aluminum hydride (135mg) was gradually added to tetrahydrofuran solution (20ml) of ethyl 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropionate (1.15g) at 0°C. After the reaction mixture was stirred for 2 hours, water was added to the reaction mixture with cooling with ice. The insoluble material was removed by filtration, and then the filtrate was concentrated. The residue was subjected to silica gel column chromatography. From the fraction eluted with

acetone-isopropyl ether (1:2, v/v), obtained was 4-(4-chlorophenyl)-2-(1-imidazolyl)-5-oxazolepropanol (690mg, 68%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 114-115°C

Example 58:

In the same manner as Example 57, obtained was 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropanol(yield: 42%) by reduction of ethyl 4-(4-chlorophenyl)-2-(1,2,4-triazol-1-yl)-5-oxazolepropionate with lithium aluminum hydride. This was recrystallized from methanol-isopropyl ether to give colorless prisms. mp 139-140°C

Example 59:

In the same manner as Example 57, obtained was 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropanol(yield: 81%) by reduction of ethyl 4-(4-chlorophenyl)-2-(2-pyridylthio)-5-oxazolepropionate with lithium aluminum hydride. This was recrystallized from diethyl ether-isopropyl ether to give colorless prisms. mp 70-71°C

Example 60:

A mixture of 4-(4-chlorophenyl)-5-(2-cyanoethyl)-2-(2-methyl-1-imidazolyl)oxazole (350mg), cysteamine (175mg) and 2-propanol was stirred under reflux for 24 hours. Water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (1:1, v/v), obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[2-(2-thiazolin-2-yl)ethyl]oxazole (320mg, 77%). This was recrystallized

from acetone-isopropyl ether to give colorless prisms. mp 73-74°C

Example 61:

In the same manner as Example 1, obtained was methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolebutyrate(yield: 69%) by reaction of methyl 4-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]butyrate with phosphorus oxychloride. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 73-74°C

Example 62:

In the same manner as Example 2, obtained was 2-chloro-4-(4-chlorophenyl)-5-oxazolebutyric acid(yield: 76%) by hydrolysis of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolebutyrate. This was recrystallized from acetone-ethyl acetate to give colorless prisms. mp 150-151°C

Example 63:

In the same manner as Example 24, obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazole butanoic acid(yield: 76%) by reaction of 2-chloro-4-(4-chlorophenyl)-5-oxazolebutyric acid with 2-methylimidazole. This was recrystallized from tetrahydrofuran-methanol to give colorless prisms. mp 211-212°C

Example 64:

In the same manner as Example 52, obtained was ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutyrate(yield: 88%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazole butyric acid with iodoethane. This was recrystallized from acetone-isopropyl ether to give colorless prisms.

mp 72-73°C

Example 65:

Lithium aluminum hydride (110mg) was gradually added to a tetrahydrofuran solution (20ml) of ethyl 4-(4-chloroethyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutyrate (960mg) at 0°C. After the mixture was stirred for 2 hours, water was added to the reaction mixture with cooling with ice. The insoluble material was removed by filtration, and then the filtrate was concentrated to obtain 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanol (750mg, 88%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 110-111°C

Example 66:

Ethyl chloroformate (375mg) was added dropwise to a tetrahydrofuran (20ml)-N,N-dimethylformamide (10ml) solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanoic acid (1.00g) and triethylamine at -30°C. After stirring for 30 minuites, the reaction mixture was added to the solution of 2-chloroethylamine (1.45g) and N,N-dimethylformamide (20ml) at 0°C. The resulting mixture was stirred for 1 hour at room temperature. Water was poured into the reaction mixture to give N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutyramide (1.00g, 85%). This was recrystallized from ethyl acetate-hexane to give colorless needles. mp 131-132°C

Example 67:

Sodium hydride (60%, oil, 130mg) was gradually added to a N,N-dimethylformamide solution (30ml) of N-(2-chloroethyl)-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutyramide (870mg) at room

temperature. After stirring for 4 hours at room temperature, the reaction mixture was poured into ice water. And this was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-oxazolin-2-yl)propyl]oxazole (615mg, 78%) was obtained by evaporating the solvent. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 88-89°C

Example 68:

Triethylamine(505mg) was added dropwise to a N,N-dimethylformamide solution of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionic acid(1.50g) and N,O-dimethylhydroxyamine hydrochloride(490mg) at 0°C. 1-Hydroxybenzotriazole hydrate(HOBt, 760mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(WSC, 950mg) were added thereto. The reaction mixture was stirred for 20 hours at room temperature. Water was poured into the reaction mixture. Saturated sodium bicarbonate solution was added to make the mixture alkaline. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The solvent was evaporated, and the precipitated crystals were collected by filtration to give N-methoxy-N-methyl-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionamide(1.54g, 91%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 116-117°C

Example 69:

A toluene solution of diisobutylaluminum hydride(DIBAL-H, 1.0M, 8.5ml) was added dropwise into a tetrahydrofuran solution (40ml) of N-methoxy-N-methyl-4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-

oxazolepropionamide(800mg) at -70°C. After the reaction mixture was stirred for 3 hours, water was added to the reaction mixture. Acetic acid was added to make the mixture neutral. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chlomatography. From the fraction eluted with ethyl acetate-hexane(1:3, v/v), obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionaldehyde(475mg, 70%). This was recrystallized from acetone-isopropyl ether ro give colorless prisms. mp 109-110°C

Example 70:

A mixture of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropionaldehyde(220mg), cysteamine(65mg), p-toluensulfonic acid monohydrate(15mg) and toluene(20ml) was stirred for 1 hour under reflux. Ethyl acetate was added to the reaction mixture. The ethyl acetate layer was separated, washed with water and then with a saturated sodium bicarbonate solution, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chlomatography. From the fraction eluted with acetone-hexane(2:1, v/v), obtained was 2-[2-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]ethyl]thiazolidine (230mg, 88%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 110-111°C

Example 71:

Methanesulfonyl chloride(215mg) was added dropwise into a tetrahydrofuran solution(20ml) of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol(200mg) and triethylamine(190mg) at room

temperature. After the reaction mixture was stirred for 12 hours, water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane(1:1, v/v), obtained was 3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl methanesulfonate(180mg, 72%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 97-98°C

Example 72:

A mixture of 3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl methanesulfonate(400mg), imidazole(140mg), potassium carbonate(280mg) and N,N-dimethylformamide(20ml) was stirred for 2 hours at 100-110°C. Water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with methanol-chloroform(5:95, v/v), obtained was 4-(4-chlorophenyl)-5-[3-(1-imidazolyl)propyl]-2-(2-methyl-1-imidazolyl)oxazole(230mg, 62%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 133-134°C

Example 73:

In the same manner as Example 72, obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(1-pyrazolyl)propyl]oxazole (yield: 54%) by reaction of 3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl methanesulfonate with pyrazole. This

was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 129-130°C

Example 74:

In the same manner as Example 38, obtained was 3-[3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl]-2,4-oxazolidinedione(yield: 89%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol with 2,4-oxazolidinedione. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 152-153°C

Example 75:

In the same manner as Example 38, obtained was 3-[3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl]-2,4-thiazolydinedione(yield: 91%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol with 2,4-thiazolidinedione. This was recrystallized from ethyl acetate-hexane to give colorless needles. mp 119-120°C

Example 76:

In the same manner as Example 38, obtained was 3-[3-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]propyl]hydantoin(yield: 65%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol with hydantoin. This was recrystallized from methanol-ethyl acetate to give colorless prisms. mp 197-198°C

Example 77:

A mixture of ethyl 2-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]-2-hydroxyacetate(1.30g) and thionyl chloride(3ml) was stirred for 30 minutes at room temperature. The

reaction mixture was concentrated. Saturated sodium bicarbonate was added to the residue, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The crystals(1.25g) obtained by evaporating the solvent was collected by filtration. Zinc powder(5.0g) was added to an acetic acid solution(10ml) of the crystals(1.25g). The resulting mixture was stirred for 1 hour at 100-110°C. The zinc powder was removed by filtration. The filtrate was concentrated. Saturated sodium bicarbonate was added to the residue, and the resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with ethyl acetate-hexane(2:3, v/v), obtained was ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazole acetate(960mg, 77%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 133-134°C

Example 78:

In the same manner as Example 57, obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolethanol (yield: 48%) by reduction of ethyl 4-(4-chlorophenyl)-2-(2-methyl-imidazolyl)-5-oxazole acetate with lithium aluminum hydride. This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 159-160°C

Example 79:

A mixture of ethyl 5-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]pentanoate(17.2g), phosphorus oxychloride(32.6g) and pyridine(4.20g) was stirred for 80 minutes at 120-130°C. The reaction mixture was

poured into ice water, and extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chlomatography. From the fraction eluted with ethyl acetate-hexane(1:3, v/v), obtained was ethyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepentanoate as an oily substance(14.1g, 78%).

NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.6-1.85(4H, m), 2.34(2H, t, J=6.5Hz), 2.86(2H, t, J=7Hz), 4.13(2H, q, J=7Hz), 7.39(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz).

Example 80:

In the same mannner as Example 79, obtained was ethyl 2-chloro-4-(4-chlorophenyl)-5-oxazolehexanoate as an oily substance (yield: 70%) by reaction of ethyl 6-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]hexanoate with phosphorus oxychloride.

NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.3-1.85(6H, m), 2.31(2H, t, J=7.5Hz), 2.85(2H, t, J=7.5Hz), 4.13(2H, q, J=7Hz), 7.39(2H, d, J=8.5Hz), 7.53(2H, d, J=8.5Hz).

Example 81:

A mixture of ethyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepentanoate(10.0g), 2-methylimidazole(7.20g), potassium carbonate(12.1g) and N,N-dimethylformamide(80ml) was stirred for 2 hours at 120-130°C. Water was added to the reaction mixture to give ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepentanoate(9.97g, 88%). This was recrystallized from ethyl acetate-isopropyl ether to give colorless prisms. mp 93-94°C

Example 82:

A mixture of ethyl 2-chloro-4-(4-chlorophenyl)-5-

oxazolehexanoate(3.53g), 2-methylimidazole(2.44g), potassium carbonate(4.10g) and N,N-dimethylformamide(50ml) was stirred for 3 hours at 120-125°C. Water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chlomatography. From the fraction eluted with ethyl acetate-hexane(1:1, v/v), obtained was ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolehexanoate as an oily substance(3.48g, 87%). NMR(δ ppm in $CDCl_3$): 1.25(3H, t, J=7Hz), 1.35-1.9(6H, m), 2.31(2H, t, J=7.5Hz), 2.77(3H, s), 2.91(2H, t, J=7.5Hz), 4.12(2H, q, J=7Hz), 7.01(1H, d, J=1.5Hz), 7.42(2H, d, J=8.5Hz), 7.48(1H, d, J=1.5Hz), 7.60(2H, d, J=8.5Hz).

Example 83:

Lithium aluminum hydride(615mg) was gradually added to a tetrahydrofuran solution(80ml) of ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepentanoate(6.00g) at 0°C. After the reaction mixture was stirred for 2 hours, water(1ml) was added to the reaction mixture with cooling with ice, and the insoluble substance was removed by filtration. The filtrate was concentrated to give 4-(4-chlorophenyl)-2-(2-methyl-imidazolyl)-5-oxazolepentanol(4.20g, 79%). This was recrystallized from ethyl acetate to give colorless prisms. mp 94-95°C

Example 84:

Lithium aluminum hydride(340mg) was gradually added to a tetrahydrofuran solution(40ml) of ethyl 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolehexanoate(3.40g) at 0°C. After the reaction

mixture was stirred for 1 hour, water(1ml) was added to the reaction mixture with cooling with ice, and the insoluble substance was removed by filtration. The filtrate was concentrated. The residue was subjected to silica gel chlomatography. From the fraction eluted with acetone-hexane(1:1, v/v), obtained was 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolehexanol(2.74g, 90%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 70-71°C

Example 85:

In the same manner as Example 71, obtained was 4-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]butyl methanesulfonate(yield: 85%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanol with methanesulfonyl chloride. This was recrystallized from acetone-diethylether to give colorless prisms. mp 100-101°C

Example 86:

Methanesulfonyl chloride(1.43g) was added dropwise to a tetrahydrofuran solution(40ml) of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepentanol(2.16g) and triethylamine(1.26g) at room temperature. After the reaction mixture was stirred for 2 hours, water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chlomatography. From the fraction eluted with acetone-hexane(1:1, v/v), obtained was 5-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]pentyl methanesulfonate as an oily substance(2.47g, 93%). NMR(δ ppm in $CDCl_3$): 1.45-1.9(6H, m), 2.78(3H, s),

2.94(2H, t, J=7.5Hz), 3.00(3H, s), 4.24(2H, t, J=6Hz), 7.01(1H, d, J=1.5Hz), 7.43(2H, d, J=8.5Hz), 7.48(1H, d, J=1.5Hz), 7.60(2H, d, J=8.5Hz).

Example 87:

In the same manner as Example 86, obtained was 6-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]hexyl methanesulfonate as an oily substance(yield: 93%) by reaction of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolehexanol with methanesulfonyl chloride. NMR(δ ppm in $CDCl_3$): 1.4-1.9(8H, m), 2.78(3H, s), 2.92(2H, t, J=7.5Hz), 3.00(3H, s), 4.23(2H, t, J=6.5Hz), 7.01(1H, d, J=1.5Hz), 7.43(2H, d, J=8.5Hz), 7.48(1H, d, J=1.5Hz), 7.61(2H, d, J=8.5Hz).

Example 88:

Diethyl azodicarboxylate(260mg) was added dropwise to a tetrahydrofuran solution(10ml) of 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanol(330mg), 1,2,4-triazole(105mg) and tributylphosphine(300mg) with cooling with ice. After stirring for 1 hour, the reaction mixture was concentrated. The residue was subjected to silica gel column chlomatography. From the fraction eluted with methanol-chloroform(5:95, v/v), obtained was 1-[4-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]butyl]1,2,4-triazole(205mg, 54%). This was recrystallized from ethyl acetate-diethyl ether to give colorless prisms. mp 74-75°C

Example 89:

A mixture of 4-[4-(4-chlorophenyl)-2-(2-methyl-imidazolyl)-5-oxazolyl]butyl methanesulfonate(600mg), imidazole(200mg), potassium carbonate(405mg) and N,N-dimethylformamide(10ml) was stirred for 90 minutes at

100-110°C. Water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with methanol-chloroform(3:97, v/v), obtained was 4-(4-chlorophenyl)-5-[4-(1-imidazolyl)butyl]-2-(2-methyl-1-imidazolyl)oxazole(310mg, 55%). This was recrystallized from ethyl acetate-diethyl ether to give colorless prisms. mp 84-85°C

Example 90:

A mixture of 5-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]pentyl methanesulfonate(2.20g), imidazole(710mg), potassium carbonate(1.43g) and N,N-dimethylformamide(40ml) was stirred for 3 hours at 80-90°C. Water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporated the solvent was subjected to silica gel column chromatography. From the fraction eluted with methanol-chloroform(3:97, v/v), obtained was 4-(4-chlorophenyl)-5-[5-(1-imidazolyl)pentyl]-2-(2-methyl-1-imidazolyl)oxazole(1.45g, 71%). The oily substance(1.45g) was dissolved in methanol(6ml), and thereto a 4N-hydrochloric acid-ethyl acetate solution (2ml) was added. Ethyl acetate was then added to the reaction mixture. The precipitated white powder was collected by filtration, and washed with ethyl acetate-acetone to give 4-(4-chlorophenyl)-5-[5-(1-imidazolyl)pentyl]-2-(2-methyl-1-imidazolyl)oxazole dihydrochloride monohydrate(1.47g, 58%). mp 197-199°C

Example 91:

A mixture of 6-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]hexyl methansulfonate(2.11g), imidazole(660mg), potassium carbonate(1.33g) and N,N-dimethylformamide(40ml) was stirred for 2 hours at 90-95°C. Water was added to the reaction mixture. The resulting mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried($MgSO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with methanol-chloroform(3:97, v/v), obtained was 4-(4-chlorophenyl)-5-[6-(1-imidazolyl)hexyl]-2-(2-methyl-1-imidazolyl)oxazole(1.26g, 64%). The oily substance (1.26g) was dissolved in methanol(5ml), and thereto a 4N-hydrochloric acid-ethyl acetate solution (1.7ml) was added. The reaction mixture was concentrated. Ethyl acetate was added to the residue. The precipitated white powder was collected by filtration. This was recrystallized from methanol-acetone to give 4-(4-chlorophenyl)-5-[6-(1-imidazolyl)hexyl]-2-(2-methyl-1-imidazolyl)oxazole dihydrochloride hemihydrate(1.16g, 49%). mp 171-173°C

Example 92:

A mixture of 4-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolyl]butyl methanesulfonate(600mg), ethyl 2-imidazolecarboxylate(410mg), potassium carbonate(405mg) and N,N-dimethylformamide (30 ml) was stirred for 2 hours at 80-90°C. Water was added to the reaction mixture. This was extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($Mg\ SO_4$). The residue obtained by evaporating the solvent was subjected to silica gel column chromatography. From the fraction eluted with acetone-hexane (1:1, v/v), obtained was ethyl 1-[4-[4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-

oxazolyl]butyl]-2-imidazolecarboxylate as crystals (460 mg, 69%). This was recrystallized from acetone-isopropyl ether to give colorless prisms. mp 134-135°C

Formulation Example 1 (production of tablets):

(1) 4-(4-Chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol (compound produced in Example 36)	30 g
(2) Lactose	50 g
(3) Corn Starch	15 g
(4) Carboxymethyl Cellulose	44 g
(5) Magnesium Stearate	1 g
1000 tablets	140 g

All of (1), (2) and (3), and 30 g of (4) were kneaded with water, then dried in vacuum and granulated. To the resulting granules, added were 14 g of (4) and 1 g of (5), mixed and tabletted, using a tabletting machine, into tablets. Thus were produced 1000 tablets each containing 30 mg/tablet of (1).

Formulation Example 2 (production of tablets):

(1) 4-(4-Chlorophenyl)-5-[2-(2-oxazolin-2-yl)ethyl]-2-(1-pyrazolyl)oxazole (compound produced in Example 51)	100 g
(2) Lactose	200 g
(3) Corn Starch	55 g
(4) Carboxymethyl Cellulose	44 g
(5) Magnesium Stearate	1 g
1000 tablets	400 g

All of (1), (2) and (3), and 30 g of (4) were kneaded with water, then dried in vacuum and granulated. To the resulting granules, added were 14 g of (4) and 1 g of (5), mixed and tabletted, using a tabletting machine, into tablets. Thus were produced

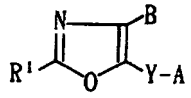
1000 tablets each containing 100 mg/tablet of (1).

INDUSTRIAL APPLICABILITY

The compounds (I) or their salts of the present invention have an excellent blood sugar-depressing effect and an insulin secretion-promoting effect, and are poorly toxic. The compounds (I) or their salts of the present invention are useful in insulin secretion promoting agents for diabetes, agents for arteriosclerosis, agents for hyperlipemia, depressors, and agents for diabetic complications (e.g., nephropathy, retinopathy, neuropathy).

CLAIMS

1. A compound represented by the formula:



wherein R^1 is a halogen atom, an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group; A is a formyl group, an optionally substituted heterocyclic group, an optionally substituted hydroxy group or an optionally esterified or amidated carboxy group; B is an optionally substituted aromatic group; Y is a divalent aliphatic hydrocarbon group; or a salt thereof.

2. A compound as claimed in claim 1, wherein R^1 is an optionally substituted heterocyclic group.

3. A compound as claimed in claim 2, wherein the heterocyclic group is a 5- or 6-membered ring having 1 to 4 atoms selected from N, O and S as the ring-constituting atoms other than carbon atom(s), or a condensed ring comprising the 5- or 6-membered ring as condensed with any of a 6-membered ring having 1 or 2 nitrogen, a benzene ring or a 5-membered ring having one sulfur.

4. A compound as claimed in claim 2, wherein the heterocyclic group is an azolyl group.

5. A compound as claimed in claim 1, wherein A is an optionally substituted heterocyclic group.

6. A compound as claimed in claim 5, wherein the

heterocyclic group is a 5- or 6-membered ring having 1 to 4 atoms selected from N, O and S as the ring-constituting atoms other than carbon atom(s), or a condensed ring comprising the 5- or 6-membered ring as condensed with any of a 6-membered ring having 1 or 2 nitrogen, a benzene ring or a 5-membered ring having one sulfur.

7. A compound as claimed in claim 5, wherein the heterocyclic group is an azolyl, azolinyl or azolidinyl group.

8. A compound as claimed in claim 2 or 5, wherein the optionally substituted heterocyclic group represented by R^1 and A is a 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrrolyl, 2-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, isoxazolyl, isothiazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-3-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, tetrazol-1-yl, tetrazol-5-yl, benzimidazol-1-yl, benzimidazol-2-yl, indol-1-yl, indol-3-yl, 1H-indazol-1-yl, 1H-pyrrolo[2,3-b]pyrazin-1-yl, 1H-pyrrolo[2,3-b]pyridin-1-yl, 1H-imidazo[4,5-b]pyridin-1-yl, 1H-imidazo[4,5-c]pyridin-1-yl, 1H-imidazo[4,5-b]pyrazin-1-yl, 1-pyrrolidinyl, piperidino, morpholino, 1-piperazinyl, hexamethyleneimin-1-yl, oxazolidin-3-yl, thiazolidin-3-yl, imidazolidin-3-yl, imidazolin-1-yl, imidazolin-2-yl, oxazolin-2-yl, thiazolin-2-yl, oxazin-2-yl, 2-oxoimidazolidin-1-yl, 2,4-dioxoimidazolidin-3-yl, 2,4-dioxooxazolidin-3-yl or 2,4-dioxothiazolidin-3-yl group which may be substituted by 1 to 3 substituents selected from the group consisting of an aliphatic

hydrocarbon group, an alicyclic hydrocarbon group, an aryl group, an aromatic heterocyclic group, a non-aromatic heterocyclic group, halogen atom, nitro group, an optionally substituted amino group, an optionally substituted acyl group, an optionally substituted hydroxy group, an optionally substituted thiol group and an optionally esterified or amidated carboxy group.

9. A compound as claimed in claim 1, wherein A is an optionally substituted hydroxy group.

10. A compound as claimed in claim 1, wherein R^1 is (1) a halogen atom,
(2) a pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, benzimidazolyl, indolyl, 1H-indazolyl, 1H-pyrrolo[2,3-b]pyrazinyl, 1H-pyrrolo[2,3-b]pyridyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-c]pyridyl, 1H-imidazo[4,5-b]pyrazinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, hexamethyleneiminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl, thiazolinyl or oxazinyl group which may be substituted by 1 to 3 substituents selected from the group consisting of

(i) a C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl group,

(ii) a C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, or C_{4-10} cycloalkadienyl group,

(iii) a C_{6-14} aryl group,

(iv) a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,

1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group,

(v) an oxiranyl, azetidinyl, oxetanyl, thietanyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl or pyrrolidinyl group,

and each of said groups (ii), (iii), (iv) and (v) may be substituted by 1 to 3 substituents selected from the group consisitng of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrahydrofuryl, morphorino, piperidino, pyrrolidino, piperazino, C_{7-9} aralkyl, amino, N-mono-C_{1-4} alkylamino, N,N-di-C_{1-4} alkylamino, C_{2-8} acylamino, amidino, C_{2-8} acyl, carbamoyl, N-mono-C_{1-4} alkyl-carbamoyl, N,N-di-C_{1-4} alkyl-carbamoyl, sulfamoyl, N-mono-C_{1-4} alkylsulfamoyl, N,N-di-C_{1-4} alkylsulfamoyl, carboxy, C_{1-7} alkoxy-carbonyl, hydroxy, C_{1-4} alkoxy, C_{2-5} alkenyloxy, C_{3-7} cyloalkyloxy, C_{7-9} aralkyloxy, C_{6-14} aryloxy, mercapto, C_{1-4} alkylthio, C_{7-9} aralkylthio, C_{6-14} arylthio, sulfo,

cyano, azido, nitro, nitroso and halogen,

(vi) halogen atom,

(vii) nitro group,

(viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{1-10} acyl and C_{6-12} aryl,

(ix) a C_{1-13} acyl group which may be substituted by a C_{1-3} alkyl, C_{1-3} alkoxy, halogen, nitro, hydroxy or amino,

(x) a hydroxy group, a C_{1-10} alkoxy group, a C_{2-10} alkenyloxy group, a C_{7-10} aralkyloxy group, a C_{2-13} acyloxy group, a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, a C_{1-10} alkylsulfonyloxy group or a C_{6-12} arylsulfonyloxy group which may be substituted by a C_{1-6} alkyl,

(xi) a mercapto or C_{1-10} alkylthio group which may be substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-

a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl, a C_{6-14} arylthio group which may be substituted by C_{1-6} alkyl, a C_{7-10} aralkylthio group, or a C_{2-13} acylthio group,

(xii) a carboxy group, a C_{1-4} alkoxy-carbonyl group, a C_{7-9} aralkyloxy-carbonyl group, a C_{6-14} aryloxy-carbonyl group, or a C_{1-4} alkoxy-carbonyl group substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl,

(xiii) a group of the formula: $-CON(R^5)(R^6)$ wherein R^5 and R^6 independently are a hydrogen; a C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl; a C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{4-10} cycloalkadienyl, C_{6-14} aryl,

furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group which may be substituted by 1 to 3 substituents selected from the group consisitng of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrahydrofuryl, morpholino, piperidino, pyrrolidino, piperazino, C_{7-9} aralkyl, amino, N-mono-C_{1-4} alkylamino, N,N-di-C_{1-4} alkylamino, C_{2-8} acylamino, amidino, C_{2-8} acyl, carbamoyl, N-mono-C_{1-4} alkylcarbamoyl, N,N-di-C_{1-4} alkylcarbamoyl, sulfamoyl, N-mono-C_{1-4} alkylsulfamoyl, N,N-di-C_{1-4} alkylsulfamoyl, carboxy, C_{2-8} alkoxycarbonyl, hydroxy, C_{1-4} alkoxy, C_{2-5} alkenyloxy, C_{3-7} cyloalkyloxy, C_{7-9} aralkyloxy, C_{6-14} aryloxy, mercapto, C_{1-4} alkylthio, C_{7-9} aralkylthio, C_{6-14} arylthio, sulfo, cyano, azido, nitro, nitroso and halogen; or a hydroxy, C_{1-10} alkoxy,

C_{2-10} alkenyloxy, C_{7-10} aralkyloxy, C_{2-13} acyloxy, C_{6-14} aryloxy which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy or C_{1-10} alkylsulfonyloxy group, and

(xiv) an oxo group,

(3) a hydroxy group, a C_{1-10} alkoxy group, a C_{2-10} alkenyloxy group, a C_{7-10} aralkyloxy group, a C_{2-13} acyloxy group, a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, a C_{1-10} alkylsulfonyloxy group or a C_{6-12} arylsulfonyloxy group which may be substituted by a C_{1-6} alkyl,

(4) a mercapto or C_{1-10} alkylthio group which may be substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl, a C_{6-14} arylthio group which may be substituted by C_{1-6} alkyl, a C_{7-10} aralkylthio group, or a C_{2-13} acylthio group, or

(5) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{1-10} acyl and C_{6-12} aryl.

11. A compound as claimed in claim 1, wherein A is (1) a formyl group, a C_{1-10} alkyl-carbonyl group, C_{3-10} cycloalkyl-carbonyl group, a C_{3-10} cycloalkenyl-carbonyl group or a C_{6-12} aryl-carbonyl group,
(2) a pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, benzimidazolyl, indolyl, 1H-indazolyl, 1H-pyrrolo[2,3-b]pyrazinyl, 1H-pyrrolo[2,3-b]pyridyl, 1H-imidazo[4,5-b]pyridyl, 1H-imidazo[4,5-c]pyridyl, 1H-imidazo[4,5-b]pyrazinyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, hexamethyleneiminyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl, thiazolinyl or oxazinyl group which may be substituted by 1 to 3 substituents selected from the group consisting of

(i) a C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl group,

(ii) a C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, or C_{4-10} cycloalkadienyl group,

(iii) a C_{6-14} aryl group,

(iv) a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl,

1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group,

(v) an oxiranyl, azetidinyl, oxetanyl, thietanyl, tetrahydrofuryl, thioranyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl or pyrrolidinyl group,

and each of said groups (ii), (iii), (iv) and (v) may be substituted by 1 to 3 substituents selected from the group consisitng of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrahydrofuryl, morphorino, piperidino, pyrrolidino, piperazino, C_{7-9} aralkyl, amino, N-mono-C_{1-4} alkylamino, N,N-di-C_{1-4} alkylamino, C_{2-8} acylamino, amidino, C_{2-8} acyl, carbamoyl, N-mono-C_{1-4} alkyl-carbamoyl, N,N-di-C_{1-4} alkyl-carbamoyl, sulfamoyl, N-mono-C_{1-4} alkylsulfamoyl, N,N-di-C_{1-4} alkylsulfamoyl, carboxy, C_{1-7} alkoxy-carbonyl, hydroxy, C_{1-4} alkoxy, C_{2-5} alkenyloxy, C_{3-7} cyloalkyloxy, C_{7-9} aralkyloxy, C_{6-14} aryloxy, mercapto, C_{1-4} alkylthio, C_{7-9} aralkylthio, C_{6-14} arylthio, sulfo, cyano, azido, nitro, nitroso and halogen,

(vi) halogen atom,

(vii) nitro group,

(viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-10} cycloalkyl, C_{1-10} acyl and C_{6-12} aryl,

(ix) a C_{1-13} acyl group which may be substituted by a C_{1-3} alkyl, C_{1-3} alkoxy, halogen, nitro, hydroxy or amino,

(x) a hydroxy group, a C_{1-10} alkoxy group, a C_{2-10} alkenyloxy group, a C_{7-10} aralkyloxy group, a C_{2-13} acyloxy group, a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, a C_{1-10} alkylsulfonyloxy group or a C_{6-12} arylsulfonyloxy group which may be substituted by a C_{1-6} alkyl,

(xi) a mercapto or C_{1-10} alkylthio group which may be substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-

b]pyridazinyl, a C_{6-14} arylthio group which may be substituted by C_{1-6} alkyl, a C_{7-10} aralkylthio group, or a C_{2-13} acylthio group,

(xii) a carboxy, a C_{1-4} alkoxy-carbonyl group, a C_{7-9} aralkyloxy-carbonyl group, a C_{6-14} aryloxy-carbonyl group, or a C_{1-4} alkoxy-carbonyl group substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl,

(xiii) a group of the formula: $-CON(R^5)(R^6)$ wherein R^5 and R^6 independently are a hydrogen; a C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl group; a C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{4-10} cycloalkadienyl, C_{6-14} aryl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-

oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group which may be substituted by 1 to 3 substituents selected from the group consisitng of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrahydrofuryl, morphorino, piperidino, pyrrolidino, piperazino, C_{7-9} aralkyl, amino, N-mono-C_{1-4} alkylamino, N,N-di-C_{1-4} alkylamino, C_{2-8} acylamino, amidino, C_{2-8} acyl, carbamoyl, N-mono-C_{1-4} alkylcarbamoyl, N,N-di-C_{1-4} alkylcarbamoyl, sulfamoyl, N-mono-C_{1-4} alkylsulfamoyl, N,N-di-C_{1-4} alkylsulfamoyl, carboxy, C_{2-8} alkoxycarbonyl, hydroxy, C_{1-4} alkoxy, C_{2-5} alkenyloxy, C_{3-7} cyloalkyloxy, C_{7-9} aralkyloxy, C_{6-14} aryloxy, mercapto, C_{1-4} alkylthio, C_{7-9} aralkylthio, C_{6-14} arylthio, sulfo, cyano, azido, nitro, nitroso and halogen; or a hydroxy, C_{1-10} alkoxy, C_{2-10} alkenyloxy, C_{7-10} aralkyloxy, C_{2-13} acyloxy, C_{6-14} aryloxy which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, or C_{1-10} alkylsulfonyloxy group,

(3) a hydroxy group, a C_{1-10} alkoxy group, a C_{2-10} alkenyloxy group, a C_{7-10} aralkyloxy group, a C_{2-13} acyloxy group, a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, a C_{1-10} alkylsulfonyloxy group or a C_{6-12} arylsulfonyloxy group which may be substituted by a C_{1-6} alkyl,
(4) a carboxy group, a C_{1-4} alkoxy-carbonyl group, a C_{7-9} aralkyloxy-carbonyl group, a C_{6-14} aryloxy-carbonyl group, or a C_{1-4} alkoxy-carbonyl group substituted by a furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl or 1,2,4-triazolo[4,3-b]pyridazinyl, or
(5) a group of the formula: $-CON(R^5)(R^6)$ wherein R^5 and R^6 independently are a hydrogen; a C_{1-10} alkyl, C_{2-10} alkenyl or C_{2-10} alkynyl group; a C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, C_{4-10} cycloalkadienyl, C_{6-14} aryl, furyl,

thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group which may be substituted by 1 to 3 substituents selected from the group consisitng of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, thienyl, furyl, pyridyl, oxazolyl, thiazolyl, tetrahydrofuryl, morphorino, piperidino, pyrrolidino, piperazino, C_{7-9} aralkyl, amino, N-mono-C_{1-4} alkylamino, N,N-di-C_{1-4} alkylamino, C_{2-8} acylamino, amidino, C_{2-8} acyl, carbamoyl, N-mono-C_{1-4} alkylcarbamoyl, N,N-di-C_{1-4} alkylcarbamoyl, sulfamoyl, N-mono-C_{1-4} alkylsulfamoyl, N,N-di-C_{1-4} alkylsulfamoyl, carboxy, C_{2-8} alkoxycarbonyl, hydroxy, C_{1-4} alkoxy, C_{2-5} alkenyloxy, C_{3-7} cyloalkyloxy, C_{7-9} aralkyloxy, C_{6-14} aryloxy, mercapto, C_{1-4} alkylthio, C_{7-9} aralkylthio, C_{6-14} arylthio, sulfo, cyano, azido, nitro, nitroso and halogen, or a hydroxy, C_{1-10} alkoxy, C_{2-10} alkenyloxy, C_{7-10} aralkyloxy, C_{2-13} acyloxy, C_{6-14}

aryloxy which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy or C_{1-10} alkylsulfonyloxy group.

12. A compound as claimed in claim 1, wherein B is a C_{6-14} aryl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl, α-carbolinyl, β-carbolinyl, γ-carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl, or 1,2,4-triazolo[4,3-b]pyridazinyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen, nitro, cyano, C_{1-6} alkoxy which may be substituted by 1 to 3 halogen, hydroxy or C_{1-6} alkoxy, C_{1-6} alkyl which may be substituted by 1 to 3 halogen, hydroxy or C_{1-6} alkoxy, C_{3-7} cycloalkyl which may be substituted by 1 to 3 halogen, hydroxy or C_{1-6} alkoxy.

13. A compound as claimed in claim 1, wherein Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms.

14. A compound as claimed in claim 1, wherein Y is a divalent aliphatic hydrocarbon group having 2 to 4 carbon atoms.

15. A compound as claimed in claim 1, wherein R^1 is (i) halogen, (ii) a imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, benzimidazolyl, pyrrolidinyl, piperidinyl, morphorinyl or hexamethyleneiminyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio, (iii) a C_{1-10} alkoxy group, (iv) a C_{6-14} aryloxy group, (v) a C_{1-10} alkylthio group, (vi) a C_{6-14} arylthio which may be substituted by a C_{1-6} alkyl, (vii) a thiol group substituted by an imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl or pyridyl group which may be substituted by a C_{1-6} alkyl or C_{6-14} aryl, (viii) a pyridyl-C_{1-4} alkylthio group, or (ix) an amino group which may be substituted by 1 or 2 C_{1-10} alkyl or C_{3-10} cycloalkyl;
A is (i) formyl group, (ii) an imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolidinyl, oxazolinyl, thiazolinyl, 2,4-dioxoimidazolidinyl, 2,4-dioxooxazolidinyl or 2,4-dioxothiazolidinyl group which may be substituted by a C_{1-10} alkyl, (iii) hydroxy group, (iv) a C_{6-14} aryloxy group which may be substituted by a C_{1-4} alkoxy, (v) a C_{1-10} alkylsulfonyloxy group, (vi) a C_{1-4} alkoxy-carbonyl group, (vii) a C_{7-9} aralkyloxy-carbonyl group, or (viii) a group of the formula: $-CON(R^5)(R^6)$, wherein R^5 and R^6 are independently hydrogen atom, C_{1-10} alkyl which may be substituted by a halogen or C_{1-10} alkoxy;
B is a phenyl group which may be substituted by a halogen; Y is $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$ or $-(CH_2)_6-$.

16. A compound as claimed in claim 1, wherein R^1 is an optionally substituted heterocyclic group; A is an optionally substituted heterocyclic group; and Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms.

17. A compound as claimed in claim 16, wherein each of the heterocyclic group represented by R^1 and A is an azolyl group, an azolinyl group or an azolidinyl group.

18. A compound as claimed in claim 16, wherein the heterocyclic group represented by R^1 is an azolyl group, and the heterocyclic group represented by A is an azolyl group, an azolinyl group or an azolidinyl group.

19. A compound as claimed in claim 16, wherein R^1 and A are independently a pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, tetrazolyl, pyrrolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, imidazolinyl, oxazolinyl or thiazolinyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl, C_{1-10} alkylthio and oxo.

20. A compound as claimed in claim 16, wherein R^1 is an azolyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio.

21. A compound as claimed in claim 20, wherein the azolyl group is an imidazolyl, pyrazolyl, 1,2,4-triazolyl, or 1,2,3-triazolyl group.

22. A compound as claimed in claim 16, wherein A is an azolyl, azolinyl or azolidinyl group which may be substituted by 1 or 2 C_{1-10} alkyl or oxo.

23. A compound as claimed in claim 16, wherein A is an imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl, thiazolidinyl, oxazolinyl, thiazolinyl, 2,4-dioxoimidazolidinyl, 2,4-dioxooxazolidinyl or 2,4-dioxothiazolidinyl group which may be substituted by a C_{1-10} alkyl.

24. A compound as claimed in claim 16, wherein B is an optionally substituted phenyl group.

25. A compound as claimed in claim 16, wherein B is a phenyl group which may be substituted by a halogen.

26. A compound as claimed in claim 16, wherein Y is a divalent aliphatic hydrocarbon group having 3 to 5 carbon atoms.

27. A compound as claimed in claim 16, wherein Y is $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$.

28. A compound as claimed in claim 1, wherein R^1 is an optionally substituted heterocyclic group; A is an optionally substituted hydroxy group; and Y is a divalent aliphatic hydrocarbon group having 1 to 7 carbon atoms.

29. A compound as claimed in claim 28, wherein the heterocyclic group represented by R^1 is an azolyl group.

30. A compound as claimed in claim 29, wherein

the azolyl group is a pyrrolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, thiazolyl, oxazolyl, 1,2,4-oxadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl or tetrazolyl group.

31. A compound as claimed in claim 28, wherein R^1 is an azolyl group which may be substituted by 1 to 3 substituents selected from the group consisting of C_{1-10} alkyl, C_{6-14} aryl and C_{1-10} alkylthio.

32. A compound as claimed in claim 31, wherein the azolyl group is an imidazolyl, pyrazolyl, 1,2,4-triazolyl or 1,2,3-triazolyl group.

33. A compound as claimed in claim 28, wherein A is (i) a hydroxy group, (ii) a C_{1-10} alkoxy group, (iii) a C_{2-10} alkenyloxy group, (iv) a C_{7-10} aralkyloxy group, (v) a C_{2-13} acyloxy group, (vi) a C_{6-14} aryloxy group which may be substituted by 1 or 2 halogen or C_{1-4} alkoxy, or (vii) a C_{1-10} alkylsulfonyloxy group.

34. A compound as claimed in claim 28, wherein A is hydroxy group.

35. A compound as claimed in claim 28, wherein B is an optionally substituted phenyl group.

36. A compound as claimed in claim 28, wherein B is a phenyl group which may be substituted by a halogen.

37. A compound as claimed in claim 28, wherein Y is a divalent aliphatic hydrocarbon group having 3 to 5 carbon atoms.

38. A compound as claimed in claim 28, wherein Y is $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$.

39. A compound as claimed in claim 1, which 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepropanol or its salt.

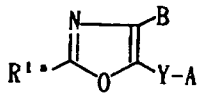
40. A compound as claimed in claim 1, which 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolebutanol or its salt.

41. A compound as claimed in claim 1, which 4-(4-chlorophenyl)-5-[3-(1-imidazolyl)propyl]-2-(2-methyl-1-imidazolyl)oxazole or its salt.

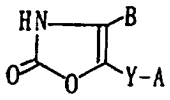
42. A compound as claimed in claim 1, which 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-oxazolepentanol or its salt.

43. A compound as claimed in claim 1, which 4-(4-chlorophenyl)-5-[4-(1-imidazolyl)butyl]-2-(2-methyl-1-imidazolyl)oxazole or its salt.

44. A process for producing a compound represented by the formula:

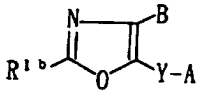


wherein R^{1a} is a halogen atom, and the other symbols are of the same meanings as defined in claim 1, or a salt thereof which comprises reacting a compound represented by the formula:

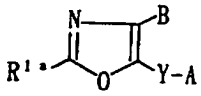


wherein all symbols are of the same meanings as defined in claim 1, or a salt thereof with a halogenating agent.

45. A process for producing compound represented by the formula:



wherein R^{1b} is an optionally substituted heterocyclic group, an optionally substituted hydroxy group, an optionally substituted thiol group or an optionally substituted amino group, and the other symbols are of the same meanings as defined in claim 1, or a salt thereof, which comprises reacting a compound represented by the formula:



wherein R^{1a} is a halogen atom, and the other symbols are of the same meanings as defined in claim 1, or a salt thereof with a compound represented by the formula:

$$R^{1b}-H$$

wherein all symbols are of the same meanings as defined above, or a salt thereof.

46. A pharmaceutical composition comprising a compound as claimed in claim 1.

47. A composition as claimed in claim 46, which

is an insulin secretion-promoting agent.

48. A composition as claimed in claim 46, which is an agent preventing and treating for diabetes.

49. Use of a compound as claimed in claim 1 for the manufacture of a medicament for the prophylaxis and treatment of diabetes.

50. Method for preventing and treating diabetes in a mammal which comprises administering to said mammal an effective amount of a compound as claimed in claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/01146

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/38 C07D263/46 C07D263/48 A61K31/42 C07D263/34
C07D413/12 C07D413/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 092 239 A (TAKEDA CHEMICAL INDUSTRIES LTD) 26 October 1983 cited in the application see claims	1,46-50
A	EP 0 382 199 A (TAKEDA CHEMICAL INDUSTRIES LTD) 16 August 1990 cited in the application see claims	1,46-50

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 1997	23.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 97/01146

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 102, no. 17, 29 April 1985 Columbus, Ohio, US; abstract no. 149257w, page 610; XP002035313 see abstract	1,46-50
A	& JP 59 190 979 A (TAKEDA CHEMICAL INDUSTRIES) 29 October 1984 cited in the application	1,46-50

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 97/01146

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 50
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-39, 44-50
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

The definition of the substituents is too general and is only partly supported by the examples given in the description. Guided by the spirit of the application the search was carried out on the basis of the examples. (CF Art.6 Guidelines Exam. Part B, chapt. III 3.6, 3.7).

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 97/01146

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0092239 A	26-10-83	JP 58183676 A	26-10-83
		AU 1355283 A	27-10-83
		CA 1195985 A	29-10-85
		US 4596816 A	24-06-86
EP 0382199 A	16-08-90	CA 2009470 A	08-08-90
		JP 2289556 A	29-11-90
		US 5239080 A	24-08-93

on the reaction, to obtain a compound (IX).

The salt of an organic acid includes, for example, sodium formate, potassium formate, and sodium acetate. The amount of the salt may be from 1 to 20 molar equivalents, preferably from about 2 to about 10 molar equivalents, relative to the compound (VIII).

The solvent that does not have any influence on the reaction includes, for example, alcohols such as methanol and ethanol.

The reaction temperature ranges generally from 0 to 150°C, preferably from about 30 to about 100°C. The reaction time ranges from 1 to 50 hours.

Next, the resulting compound (IX) is reacted with a chlorocarbonate to obtain a compound (X). This reaction may be conducted in any ordinary manner, in the presence of a base in a solvent that does not have any influence on the reaction.

The base includes, for example, alkali metal salts such as potassium hydroxide, sodium hydroxide, sodium hydrogencarbonate and potassium carbonate; and amines such as pyridine, triethylamine and N,N-dimethylaniline. The amount of the base to be used may be preferably from 2 to 5 molar equivalents relative to the compound (IX).

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene, toluene and xylene; ethers such as tetrahydrofuran and dioxane; halogenated hydrocarbons such as chloroform and dichloromethane; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The reaction temperature ranges generally from -50°C to 150°C, preferably from about -30°C to about 50°C. The reaction time ranges from 0.5 to 20 hours.

Next, the compound (X) is reacted with ammonia or its salt to obtain the intended compound (II). This

reaction may be conducted generally in the presence of a solvent that does not have any influence on the reaction.

The ammonia or its salt includes, for example, ammonia gas, and ammonium acetate. For example, when such an ammonium salt is used, its amount may be from 1 to 20 molar equivalents relative to the compound (X).

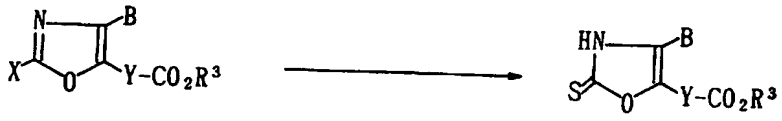
The solvent that does not have any influence on the reaction includes, for example, ethers such as tetrahydrofuran and dioxane; acetic acid; and mixed solvents of these.

The reaction temperature ranges generally from 0 to 150°C, preferably from about 50 to about 120°C. The reaction temperature ranges from 0.5 to 20 hours.

The compounds (II) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

The starting compounds (III) for the Method D can be produced, for example, by the following method S.

Method S:



(I-1) (III)

wherein all symbols are of the same meanings as those mentioned above.

The compounds (III) can be produced by reacting a compound (I-1) with thiourea, thioacetic acid or its salt, in the presence of a base in a suitable solvent that does not have any influence on the reaction.

The base includes, for example, alkali metal salts

such as potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium hydrogencarbonate, and potassium carbonate.

The solvent that does not have any influence on the reaction includes, for example, ethers such as tetrahydrofuran and dioxane; N,N-dimethylformamide, dimethylsulfoxide; and mixed solvents of these.

The amount of thiourea, thioacetic acid or its salt to be used may be from 1 to 20 molar equivalents, preferably from about 2 to about 10 molar equivalents, relative to the compound (I-1).

The reaction temperature ranges generally from 0 to 150°C, preferably from about 50 to about 120°C. The reaction time ranges from 0.1 to 20 hours.

The compounds (III) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

The starting compounds (IV) for the Method H can be produced, for example, by the following method T.

Method T:

(I-8)

(IV: E is halogen)
(I-20: E is OSO_2R^4)

wherein all symbols are of the same meanings as those mentioned above.

The compound (IV), wherein E is halogen, can be produced by reacting a compound (I-8) with a halogenating agent, and the compound (IV), wherein E is OSO_2R^4, can be produced by reacting a compound (I-8)

with a sulfonylating agent.

Where a halogenating agent is used, it is preferably thionyl chloride, phosphorus tribromide or the like. In this case, produced are the compounds (IV) where E is chlorine or bromine. The amount of the halogenating agent to be used may be from about 1 to about 20 molar equivalents relative to the compound (I-8).

The reaction may be effected generally in a solvent that does not have any influence on the reaction (e.g., benzene, toluene, chloroform, dichloromethane). If desired, an excess amount of the halogenating agent may be used for the solvent.

The reaction temperature ranges generally from -20°C to 150°C, preferably from about 10 to about 100°C. The reaction time ranges 0.1 to 20 hours.

Where a sulfonylating agent is used, it is preferably mesyl chloride, tosyl chloride, benzenesulfonyl chloride or the like. In this case, produced are the compounds (I-20) where E is a mesyloxy, tosyloxy or benzenesulfonyloxy group, respectively.

The reaction may be conducted generally in the presence of a solvent that does not have any influence on the reaction, preferably in the presence of a suitable base.

The solvent that does not have any influence on the reaction includes, for example, aromatic hydrocarbons such as benzene and toluene; halogenated hydrocarbons such as chloroform and dichloromethane; ethyl acetate, and tetrahydrofuran.

The base includes, for example, triethylamine, N-methylmorpholine, N,N-dimethylaniline, sodium hydrogencarbonate, potassium carbonate, and sodium carbonate.

The amount of the sulfonylating agent and that of

the base to be used may be from about 1 to about 1.5 molar equivalents each, relative to the compound (I-8).

The reaction temperature ranges generally from -20°C to 150°C, preferably from about 10 to about 100°C. The reaction time ranges from 0.1 to 20 hours.

The compounds (IV) thus produced may be isolated and purified through any ordinary separating and isolating means such as concentration, concentration under reduced pressure, solvent extraction, precipitation, recrystallization, phasic transfer, chromatography or the like.

BEST MODE FOR CARRYING OUT THE INVENTION

Now, the present invention is described in more detail hereinunder, with reference to the following test example, reference examples, examples and formulation examples, which, however, are not intended to restrict the scope of the invention. In the following reference examples and examples, % is by weight unless otherwise specifically indicated.

Experimental Example 1:

Test for Blood Sugar Depression in Mice:

After being fasted for 20 hours, 9- to 12-week-old, male KKA^y mice (five mice in each group) were orally given the test compound at a dose of 30 mg/kg/10 ml through a stomach tube. Control mice were orally given 5% gum arabic solution. Blood samples (70µl) were obtained from orbital venous plexus through capillary tube before and 60 and 120 minutes after the administration of the test compound. Blood glucose was determined according to a glucose oxidase method using a commercial kit (Iatrochem, GIU(A), Iatron Labs. Inc.). Blood glucose level at 60 or 120 minutes of the test groups was compared with that of control group, and was shown as blood glucose depression (%) (Table

1).

Table 1

Test Compound (Example Number)	Degree of Blood Glucose Depression (%)	
	After 60 minutes	After 120 minutes
15	22	26
25	38	27
26	32	27
28	24	33
31	27	28
32	25	28
34	27	25
36	23	18

As demonstrated in the above table 1, the compounds (I) of the present invention have a blood sugar (blood glucose) depressing effect and are useful in agents for diabetes.

Experimental Example 2

Insulinotropic effect on MIN6 cells

MIN6 cells established from mouse beta cell tumor were cultured in DMEM supplemented with 15 % fetal bovine serum on 12-well plate at 37 °C in 5 % CO_2, and were used at the stage of subconfluency. Cells were washed twice with PBS and incubated in Krebs-Ringer HEPES(KRH) containing with 0.1 mM glucose for 30 minutes. Then they were incubated in KRH containing with 12.5 mM glucose and 0.1 % DMSO (control) or compound (10μM) for 2 hours. Medium was collected and insulin concentration was measured using a commercial radioimmunoassay kit (Amarsham Inc.). The plate was washed once with PBS and cellular protein content was determined by the method of Lowrey et al.(J. Biol. Chem. 193, 265-275, 1951). Insulinotropic activity of

the compound was indicated as percentage of control (Table 2).

Table 2

Test Compound (Example Number)	Insulin secretion-promoting effect (%)
36	272
65	397
72	303
83	359
89	385

As demonstrated in the above Table 2, the compounds (I) of the present invention have insulin secretion-promoting effect and are useful in agents for diabetes.

Reference Example 1:

Bromine (46.5 g) was added dropwise to a dichloromethane (400 ml) solution of methyl 4-(4-chlorobenzoyl)butyrate (70.0 g). After stirring for 15 minutes, the reaction mixture was washed with water, dried ($MgSO_4$), and concentrated to obtain methyl 4-bromo-4-(chlorobenzoyl)butyrate (89.5 g, 96 %) as an oily substance. NMR (δ ppm in $CDCl_3$): 2.3-2.7(4H,m), 3.71(3H,s), 5.33(1H,dd,J=8&5.5Hz), 7.48(2H,d,J=8.5Hz), 7.98(2H,d,J=8.5Hz).

Reference Example 2:

A mixture of methyl 4-bromo-4-(chlorobenzoyl)butyrate (89.5 g), sodium formate (76.2 g) and methanol (400 ml) was stirred under reflux for 12 hours. The reaction mixture was concentrated, and water was added to the resulting residue and then

extracted with ethyl acetate. The ethyl acetate layer was washed with water, and dried ($MgSO_4$). The solvent was evaporated to give methyl 4-(chlorobenzoyl)-4-hydroxybutyrate (72.0 g, 100 %) as an oily substance. This oily substance (72.0 g) was dissolved in tetrahydrofuran (400 ml), pyridine (22.2 g) was added thereto, and thereafter phenyl chlorocarbonate (43.8 g) was dropwise added thereto with cooling with ice. After the reaction mixture was stirred at room temperature for 1 hour, water was added to the reaction mixture and then extracted with ethyl acetate. The ethyl acetate layer was washed with 2 N hydrochloric acid and then with water, and dried ($MgSO_4$). The solvent was evaporated, and the crystals thus precipitated were collected by filtration to obtain methyl 4-(4-chlorobenzoyl)-4-phenoxycarbonyloxybutyrate (61.2 g, 58 %). This was recrystallized from methanol to give colorless prisms. mp 97-98°C.

Reference Example 3:

A mixture of methyl 4-(4-chlorobenzoyl)-4-phenoxycarbonyloxybutyrate (61.2 g), ammonium acetate (62.2 g) and acetic acid (300 ml) was stirred under reflux for 1.5 hours. The reaction mixture was concentrated, water was added to the resulting residue, and the crystals thus precipitated were collected by filtration. These were recrystallized from methanol to give colorless needles of methyl 3-[4-(4-chlorophenyl)-2-oxo-4-oxazolin-5-yl]propionate (36.6 g, 79 %). m.p. 147-148°C.

Reference Example 4:

A mixture of methyl 2-chloro-4-(4-chlorophenyl)-5-oxazolepropionate (5.72 g), thiourea (4.57 g) and ethanol (70 ml) was stirred under reflux for 30 minutes. An aqueous solution of 2 N sodium hydroxide